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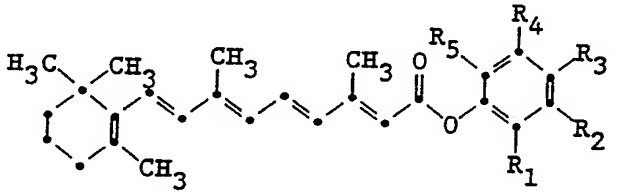
(54) Title: COMPOUND AND METHOD FOR TREATING SKIN FOR ACNE OR PSORIASIS



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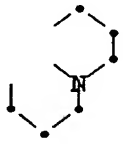
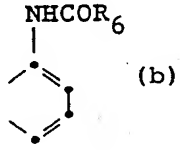


(a)



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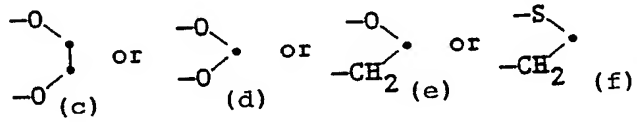

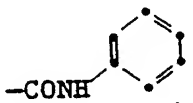

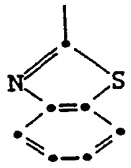

(57) Abstract

The effects of acne and psoriasis are relieved by applying either topically or by oral administration, a compound having structure(I), wherein R_1, R_2, R_3, R_4, and R_5 are independently selected from the group consisting of H, Cl, straight or branched alkyl of 1 to 10 carbon atoms, NO_2, $COOR_6$, CN, OR_6, NR_6R_7, $NR_6C(=S)NR_7R_8$, NR_6COR_7, $SO_2NR_6R_7$, $CH(CH_3)COOH$, $CONR_6R_7$, COR_6, $OCONR_6R_7$, NR_6COONR_7, R_9OR_6, $NR_6SO_2R_7$, $Si(CH_3)_3$, and $NR_6CONR_7R_8$, R_3 together with R_4 forms a benzo ring or taken together with R_2 forms a benzo or tetrahydrobenzo ring or together with R_2 and R_1 forms a (a) moiety or together with R_2 forms a (b) moiety or R_2 together with R_1 forms a benzo ring or R_2 together with R_3 forms a (c) or (d) or (e) or (f) moiety, or R_1 is independently selected from the group consisting of (g), (h) moiety, R_6, R_7 and R_8 are independently selected from the group consisting of straight or branched alkyl containing from 1 to 10 carbon atoms, aryl containing from 6 to 10 carbon atoms and hydrogen, and R_9 is alkylene of 1 to 6 carbon atoms, and iron carbonyl complexes thereof, to an area of the human skin in an amount effective to repair damage due to acne or psoriasis. This treatment is not accompanied by substantial discomfort or dermatological irritation.

* See back of page

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COMPOUND AND METHOD FOR TREATING SKIN FOR ACNE OR PSORIASIS

Cross-Reference to Related Applications

This application is a Continuation-In-Part of copending U.S. Application Serial No. 384,948 filed on July 25, 1989.

Field of the Invention

This invention relates to a compound and a method of treating skin diseases relating to acne and/or psoriasis by application, either topical or by oral ingestion of specific polyene compositions.

Background of the Invention

Acne is a dermatological disorder which is more prevalent in adolescence and is found mainly within the age group of about 15 to 22. As it occurs primarily in the face and trunk areas, affecting the appearance of the patient, it probably causes more mental pain and anguish to those afflicted than many other diseases which, from a physical standpoint, may be much more severe. The basic lesion of acne is the comedo or "blackhead" of a pilosebaceous follicle. The condition may be mild and transient with only a few blackheads which can easily be ejected by pressure and are of little concern, or may be severe, persistent, and very disfiguring with the more serious cases frequently leaving permanent scarring.

There have been many treatments proposed for acne, almost any treatment giving some relief. What appears to occur in the development of acne is that there is an initial filling up of the follicle with a rather tough, keratinous material. The impactation of horny material is the whitehead and blackhead. As a result of bacterial growth in these horny impactations, the follicle ruptures initiating the inflammatory phase of the disease which takes the form of pustules, papules, cysts and nodules.

One of the commonly used methods for acne treatment is the use of peeling agents which cause exfoliation with the removal of some of the keratinous plugs. In the more serious cases where pustular or cystic lesions exist, the same are evacuated by incision and the contents expressed. Various other therapies have been employed, such as vaccine therapy, to assist in the control of chronic infection and increase the patient's resistance to Staphylococcis; hormone therapy, which is applicable only for female patients who may be put on routine contraceptive regimen with estrogen; antibacterial therapy for the treatment of extensive pustular or cystic acne where the patient may be treated with tetracyclines, penicillin, erythromycin, or other of the antibacterial agents and, in some instances, general surgical skin planing may be used.

The administration of large oral doses of vitamin A has been suggested as being beneficial in acne, Staumford, J. V.: "Vitamin A: Its Effects on Acne," Northwest Med., 42; 219–225, August 1943), although other investigators have felt it to be ineffective (Anderson, J. A. D. et al, "Vitamin A in Acne Vulgaris," Brit. Med. J. 2: 294–296, August 1963; Lynch, F. W. et al, "Acne Vulgaris Treated With Vitamin A," Arc Derm. 55: 355, 357, March 1947, and Mitchell, G. H. et al, "Results of Treatment of Acne Vulgaris by Intramuscular Injections of Vitamin A," Arch. Derm., 64: 428–430, October 1951).

Vitamin A acid has been applied topically. Beer (Beer, Von P., "Untersuchungen über die Wirkung der Vitamin A–Saure," Dermatologica, 124: 192–195, March 1962) and Stüttgen (Stüttgen, G., Zur Lokalbehandlung von Keratosen mit Vitamin A–Saure," Dermatologica, 124: 65–80, February 1962) reported achieving good results in those hyperkeratotic disorders which

are responsive to high oral doses of Vitamin A. Among those treated by Beer and Stüttgen were patients with acne; however, these investigators reported no effective results on this disorder.

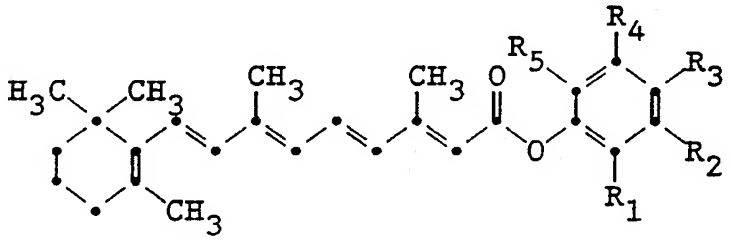
British Patent 906,005 discloses a cosmetic peparation containing vitamin A acid for regulation of the cornification processes of human-skin. However, this treatment also results in great irritation to the skin, which severely limits its usefullness.

In U.S. Patent 4,595,696 certain polyenes are described as being useful in treating inflammatory or allergic conditions. These conditions are far afield of acne and materials useful for the treatment of inflammatory conditions are not expected to be useful in the treatment of acne and vice versa.

In addition, it has been reported in "Arotinoid Ro 13-6298 and Etretin: Two New Retinoids Inferior to Isotretinoin in Sebrum Suppression and Acne Treatment", by Harms, M. et al, Acta Derm Venereol (Stockh) 1986; 66: 149-154, that extremely close analogs of retinoic acid are not effective in the treatment of acne. This illustrates the unpredictability of these compounds to treat acne.

Summary of the Invention

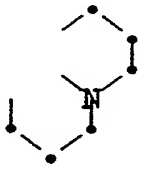
The present invention relates to a method of treating acne or psoriasis comprising administering a compound having the structure:



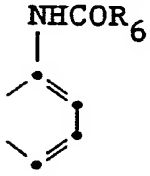
wherein

R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of H, Cl, straight or branched alkyl of 1 to 10 carbon atoms, NO_2, $COOR_6$, CN, OR_6, NR_6R_7, $NR_6C(=S)NR_7R_8$, NR_6COR_7, $SO_2NR_6R_7$, $CH(CH_3)COOH$, $CONR_6R_7$, COR_6, $OCONR_6R_7$, NR_6COONR_7, R_9OR_6, $NR_6SO_2R_7$, $Si(CH_3)_3$, and $NR_6CONR_7R_8$,

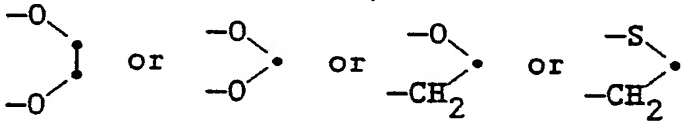
R_3 together with R_4 forms a benzo ring or taken together with R_2 forms a benzo or tetrahydrobenzo ring or together with R_2 and R_1 forms a:



moiety or together with R_2 forms a

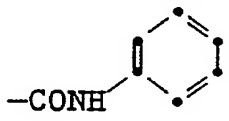


moiety or R_2 together with R_1 forms a benzo ring or R_2 together with R_3 forms a



moiety, or

R_1 is independently selected from the group consisting of



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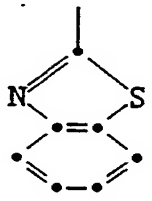
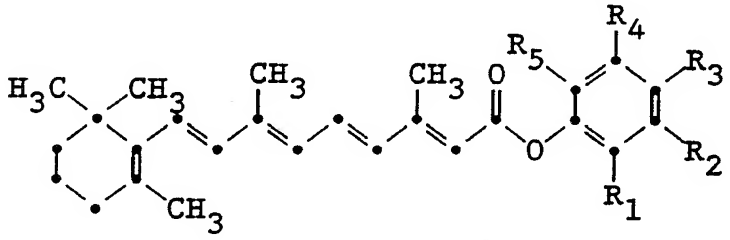


moiety,

R_6, R_7 and R_8 are independently selected from the group consisting of straight or branched alkyl containing from 1 to 10 carbon atoms, aryl containing from 6 to 10 carbon atoms and hydrogen, and

R_9 is alkylene of 1 to 6 carbon atoms, and iron carbonyl complexes thereof, to an area of the human skin in an amount effective to repair damage due to acne or psoriasis.

The present invention also provides novel polyenes within the scope of the foregoing structural formula that are useful for topical treatment of acne or psoriasis. More particularly, the novel polyenes of the present invention have the structure:



wherein

R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of H, Cl, NO_2, CN, OR_6, $NR_6C(=S)NR_7R_8$, $SO_2NR_6R_7$, $CH(CH_3)COOH$, $OCONR_6R_7$, NR_6COONR_7, R_9OR_6, $NR_6SO_2R_7$, $Si(CH_3)_3$, $NR_6CONR_7R_8$, NR_6COR_7, with the proviso that where R_3 is $NHCOR_7$, and R_1 and R_2 are hydrogen R_7 cannot be methyl,

straight or branched alkyl of 1 to 10 carbon atoms, with the proviso where R_1 is alkyl, the alkyl cannot contain an acetal,

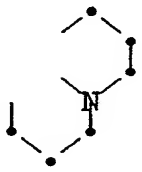
$COOR_6$, with the proviso that where R_1 is $COOR_6$, R_6 is not hydrogen or methyl, and that where R_3 is $COOR_6$, R_6 is not ethyl,

NR_6R_7, with the proviso that where R_1 or R_3 are NR_6R_7, R_6 and R_7 are not both hydrogen,

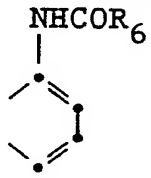
$CONR_6R_7$, with the proviso that where R_1 is $CONR_6R_7$, R_6 and R_7 are not both hydrogen, and ,

COR_6, with the proviso that where R_3 is COR_6, R_6 is not hydrogen,

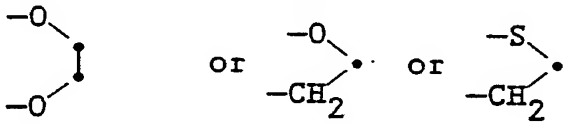
R_3 together with R_4 forms a benzo ring or taken together with R_2 forms a benzo or tetrahydrobenzo ring or together with R_2 and R_1 forms a:



moiety or together with R_2 forms a

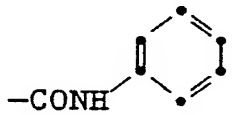


moiety or R_2 together with R_1 forms a benzo ring or R_2 together with R_3 forms a



moiety, or

R_1 is independently selected from the group consisting of



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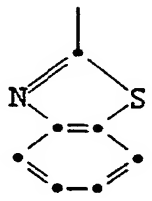


moiety,

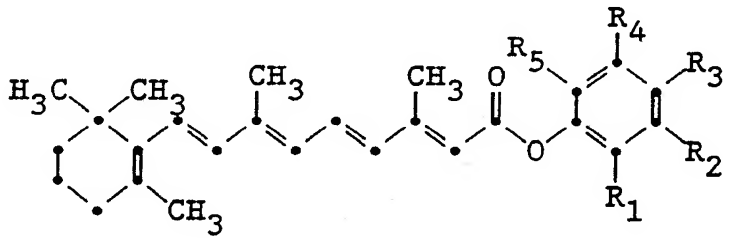
R_6, R_7 and R_8 are independently selected from the group consisting of straight or branched alkyl containing from 1 to 10 carbon atoms, aryl containing from 6 to 10 carbon atoms and hydrogen, and

R_9 is alkylene of 1 to 6 carbon atoms, and iron carbonyl complexes thereof.

Detailed Description of the Preferred Embodiments

The treatment of skin with the polyenes of the present invention aid in clearing acne in the skin.

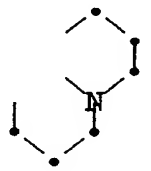
The method of treating acne or psoriasis of this invention comprises administering a compound having the structure:



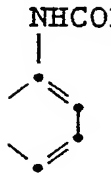
wherein

R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of H, Cl, straight or branched alkyl of 1 to 10 carbon atoms, NO_2, $COOR_6$, CN, OR_6, NR_6R_7, $NR_6C(=S)NR_7R_8$, NR_6COR_7, $SO_2NR_6R_7$, $CH(CH_3)COOH$, $CONR_6R_7$, COR_6, $OCONR_6R_7$, NR_6COONR_7, R_9OR_6, $NR_6SO_2R_7$, $Si(CH_3)_3$, and $NR_6CONR_7R_8$,

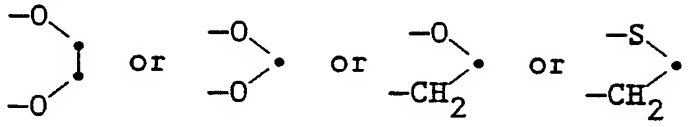
R_3 together with R_4 forms a benzo ring or taken together with R_2 forms a benzo or tetrahydrobenzo ring or together with R_2 and R_1 forms a:



moiety or together with R_2 forms a

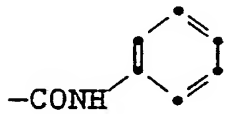


moiety or R_2 together with R_1 forms a benzo ring or R_2 together with R_3 forms a



moiety, or

R_1 is independently selected from the group consisting of



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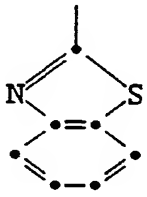
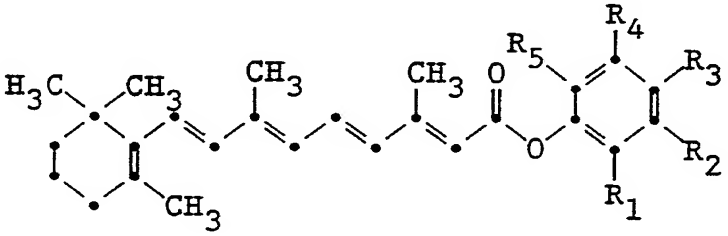


moiety,

R_6, R_7 and R_8 are independently selected from the group consisting of straight or branched alkyl containing from 1 to 10 carbon atoms, aryl containing from 6 to 10 carbon atoms and hydrogen.

The novel polyene compounds of the present invention have the structure:



wherein

R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of

H, Cl, NO_2, CN, OR_6, $NR_6C(=S)NR_7R_8$, $SO_2NR_6R_7$, $CH(CH_3)COOH$, $OCONR_6R_7$, NR_6COONR_7, R_9OR_6, $NR_6SO_2R_7$, $Si(CH_3)_3$, $NR_6CONR_7R_8$, NR_6COR_7, with the proviso that where R_3 is $NHCOR_7$, and R_1 and R_2 are hydrogen, R_7 cannot be methyl,

straight or branched alkyl of 1 to 10 carbon atoms, with the proviso where R_1 is alkyl, the alkyl cannot contain an acetal,

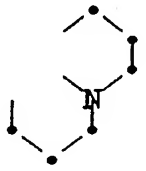
$COOR_6$, with the proviso that where R_1 is $COOR_6$, R_6 is not hydrogen or methyl, and that where R_3 is $COOR_6$, R_6 is not ethyl,

NR_6R_7, with the proviso that where R_1 or R_3 are NR_6R_7, R_6 and R_7 are not both hydrogen,

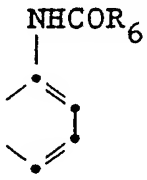
$CONR_6R_7$, with the proviso that where R_1 is $CONR_6R_7$, R_6 and R_7 are not both hydrogen, and ,

COR_6, with the proviso that where R_3 is COR_6, R_6 is not hydrogen,

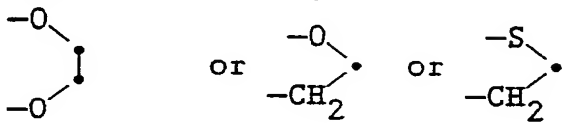
R_3 together with R_4 forms a benzo ring or taken together with R_2 forms a benzo or tetrahydrobenzo ring or together with R_2 and R_1 forms a:



moiety or together with R_2 forms a

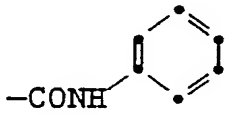


moiety or R_2 together with R_1 forms a benzo ring or R_2 together with R_3 forms a

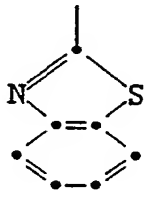


moiety, or

R_1 is independently selected from the group consisting of



,

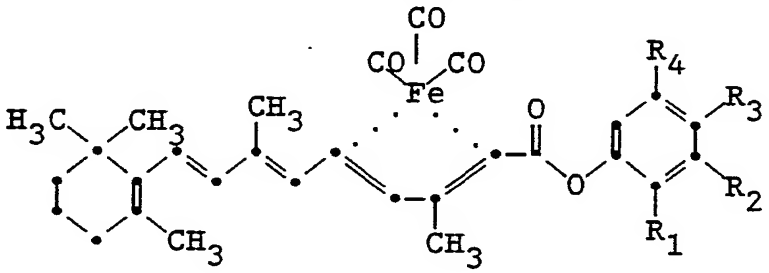


moiety,

R_6, R_7 and R_8 are independently selected from the group consisting of straight or branched alkyl containing from 1 to 10 carbon atoms, aryl containing from 6 to 10 carbon atoms and hydrogen, and

R_9 is alkylene of 1 to 6 carbon atoms, such as methylene, propylene, butylene, trimethylene, etc.,

and iron carbonyl complexes thereof such as



The preferred compounds of the invention include compounds having the above structure and formula wherein R_2 and R_3 are independently selected from the group consisting of NR_6COR_7, $CONR_6R_7$, $SO_2NR_6R_7$, $OCONR_6R_7$,

NR_6COOR_7, $NR_6CONR_7R_8$, $NR_6SO_2R_7$ and $NR_6C(=S)NR_7R_8$.

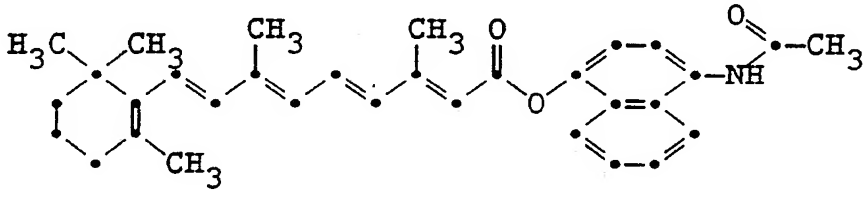
For the purposes of this invention, examples of alkyl of 1 to 10 carbon atoms for R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are methyl, butyl, pentyl, octyl, ethyl, tertiary-butyl, benzyl, isopropyl, chloroethyl, chloropropyl, hydroxypropyl, carboxyethyl, carboxymethyl, phenynyl, cyanoethyl, and 2-ethylhexyl. Aryl groups containing 6 to 10 carbon atoms as defined in R_6, R_7, R_8 hereinabove are exemplified by phenyl and naphthyl.

The novel polyenes representative of the invention include, but are not limited to Compounds I, III-XXII, XXIV, XXVI-XLIII, and XLV-LII described more fully hereinafter.

The method of preparing these polyenes is well known and is generally described in U.S. Patent 4,595,696(incorporated herein by reference). Generally, the compounds are formed by reaction of polyene acids with acetic anhydride, boron trifluoride, oxalkylene chloride, phosphorous trichloride, thionyl chloride or a haloformate and then further treated with phenolic compounds.

Polyenes useful for carrying out the present invention include those with the following structures:

I.



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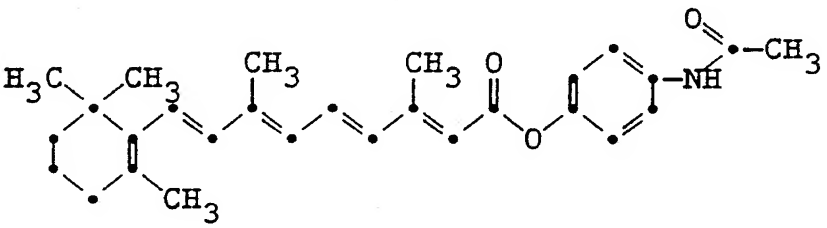

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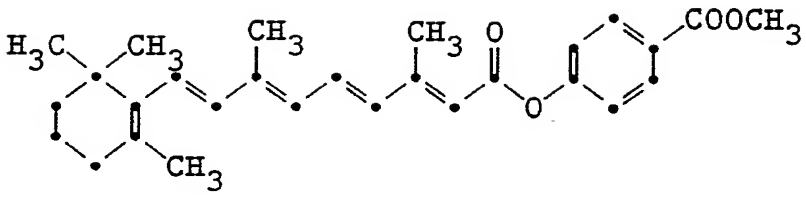

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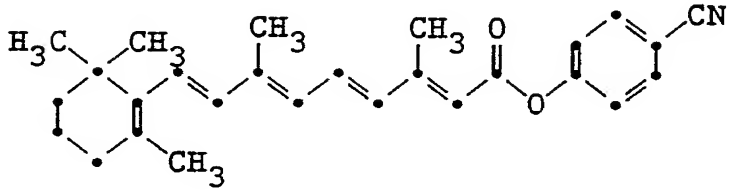

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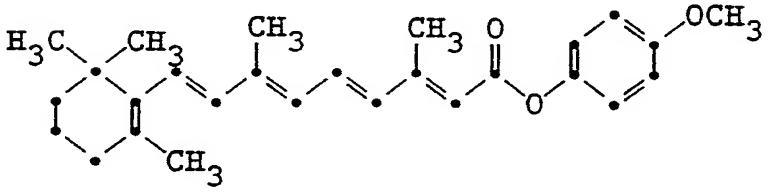

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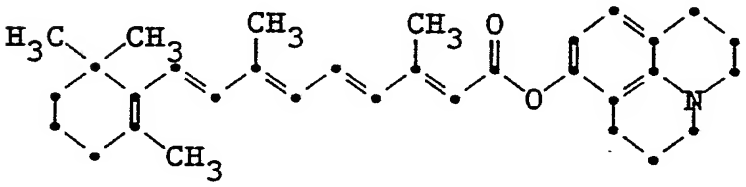

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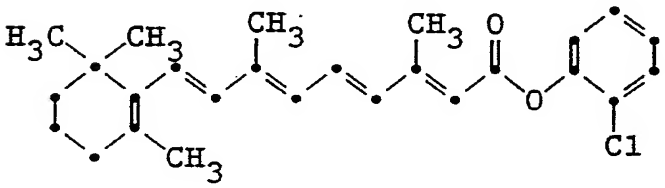

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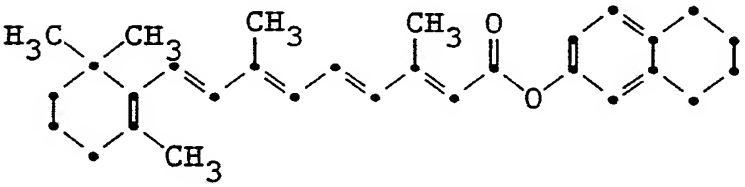

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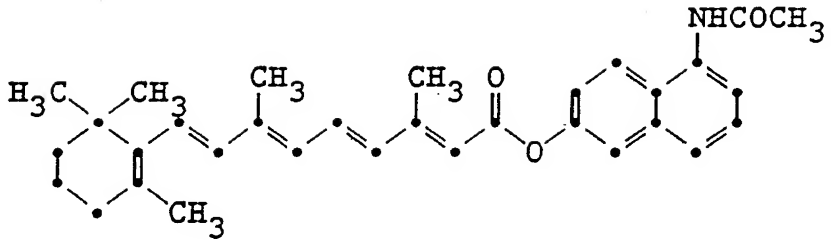
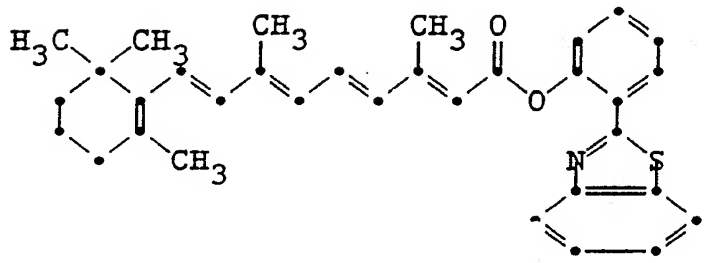


X.



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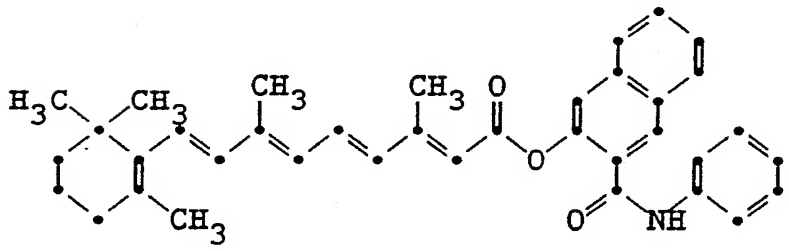

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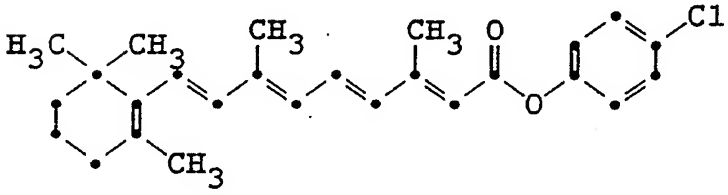

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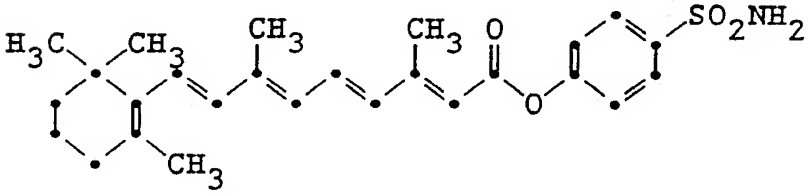

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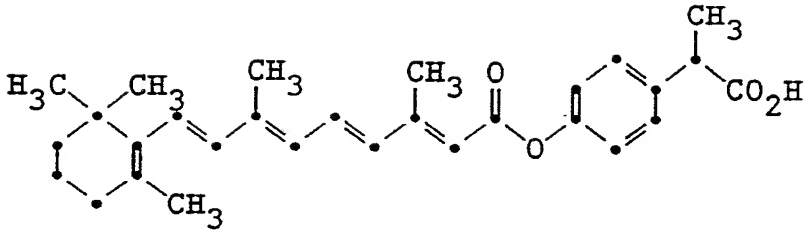

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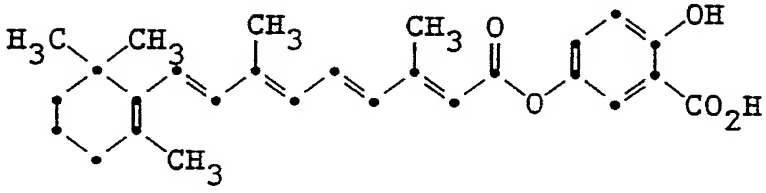

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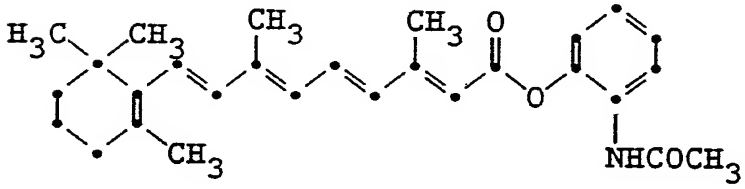

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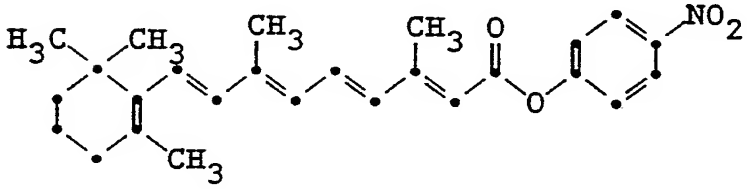

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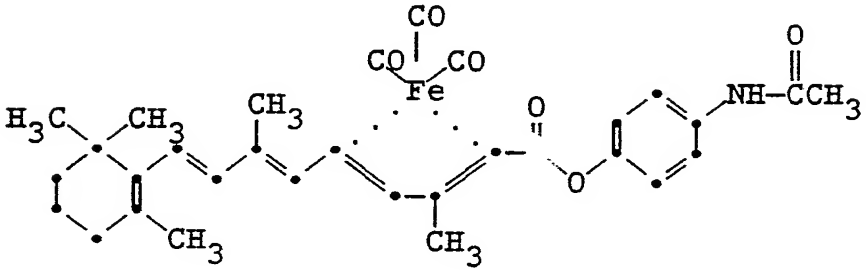

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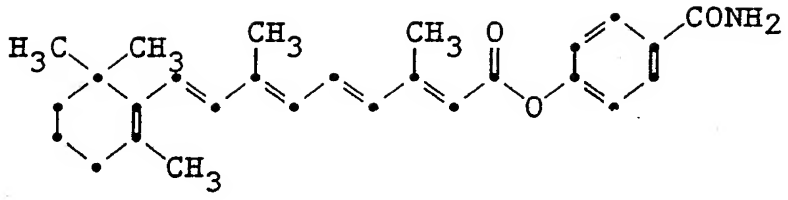

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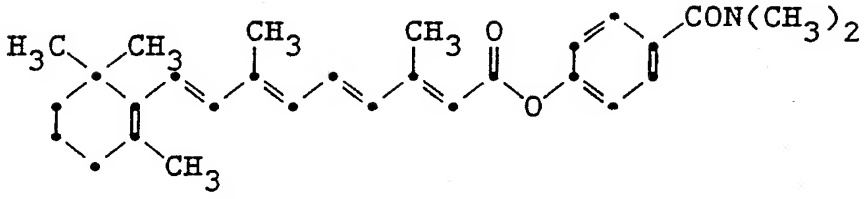

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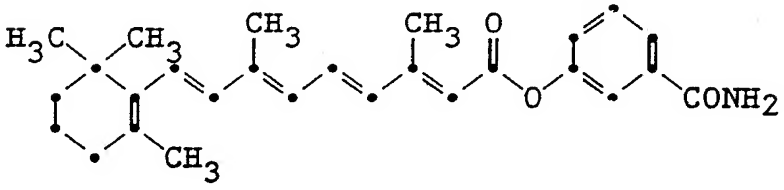

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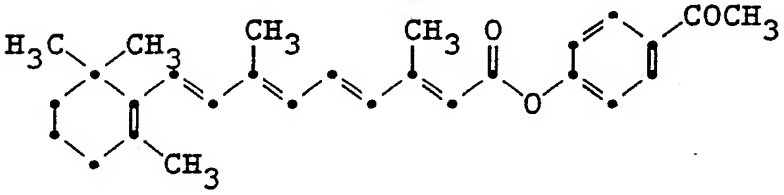

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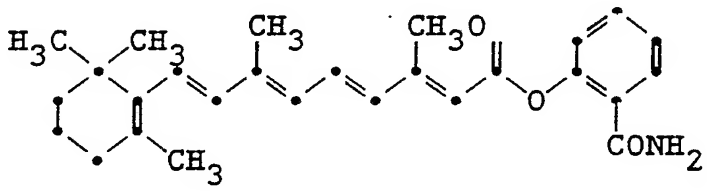

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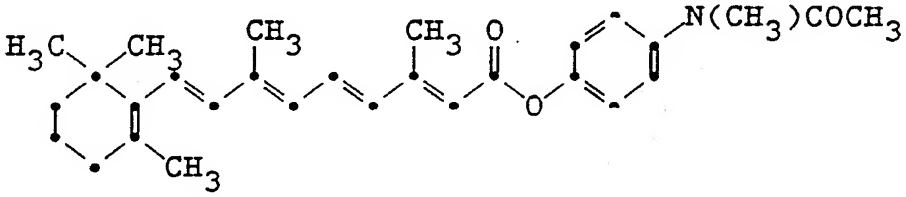

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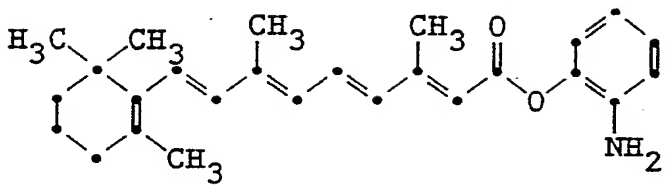

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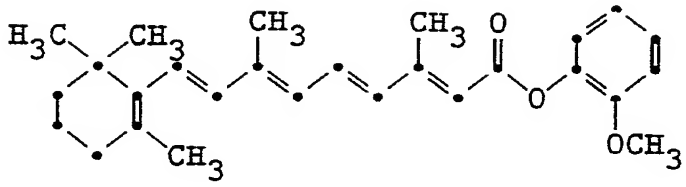

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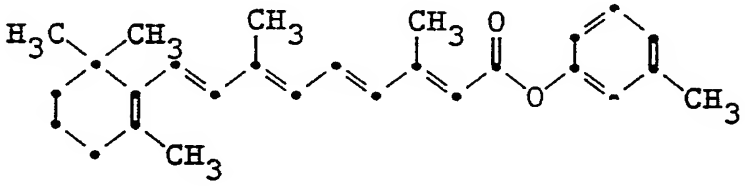

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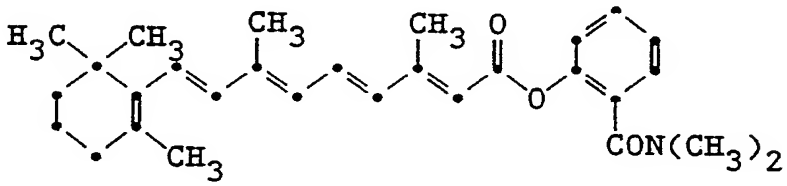

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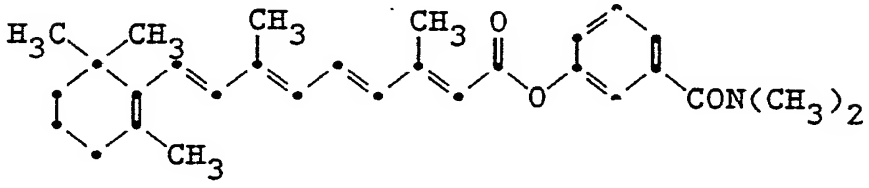

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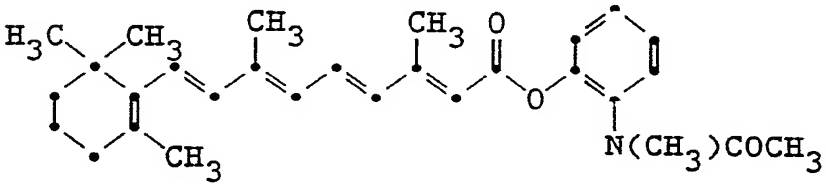

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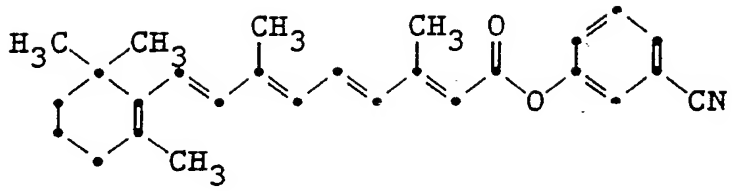

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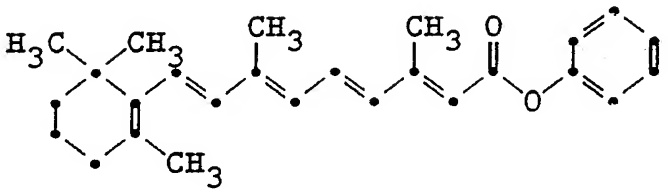

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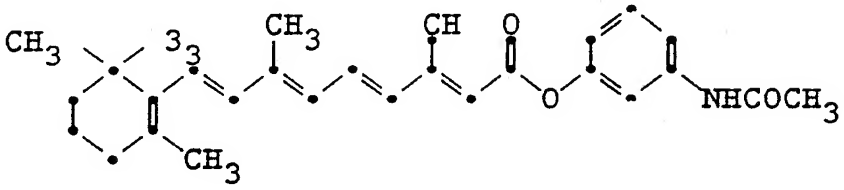

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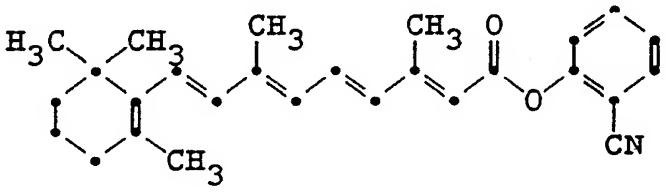

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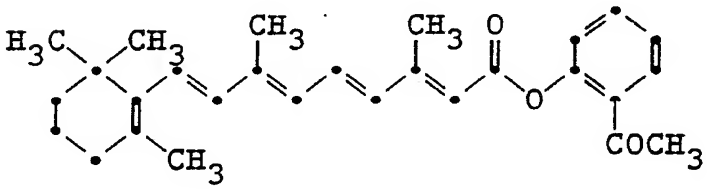

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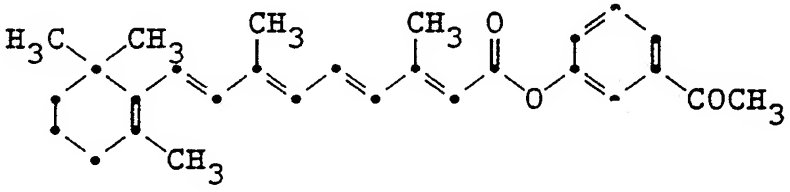

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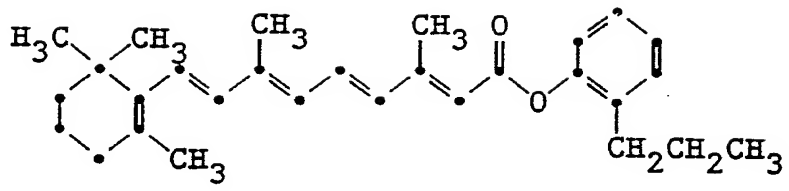

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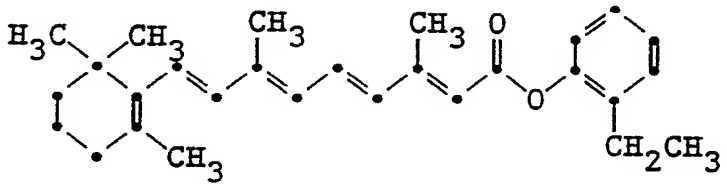

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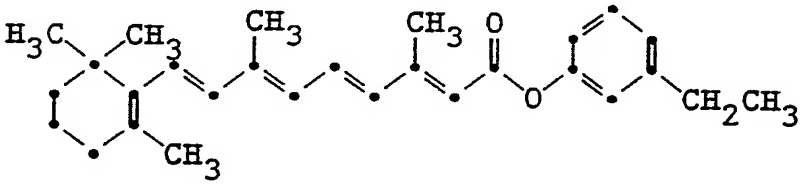

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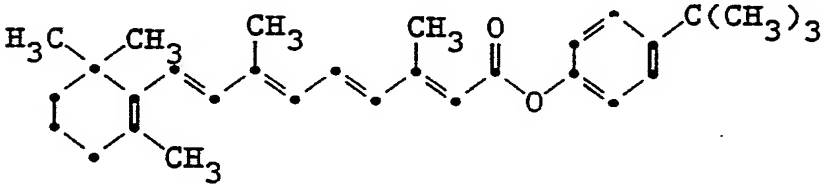

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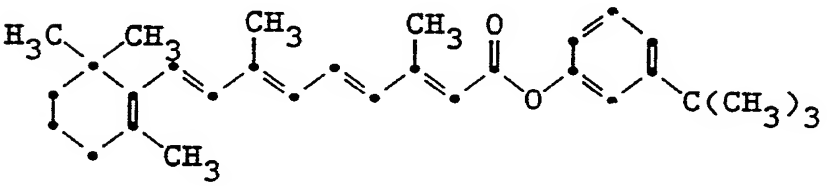

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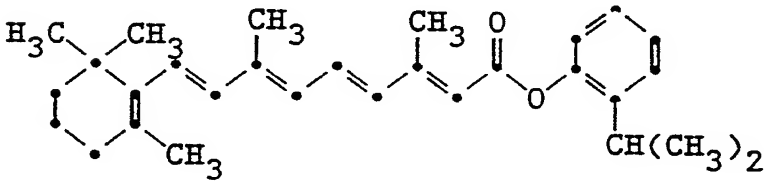

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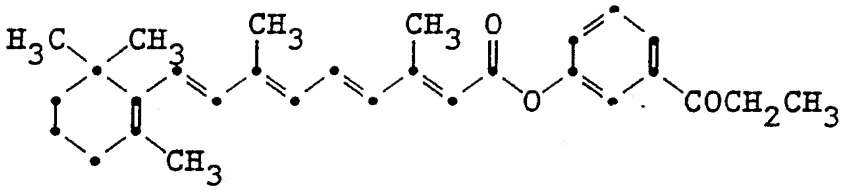

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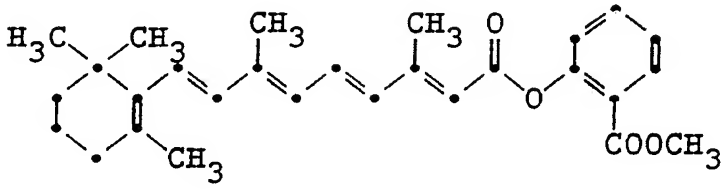

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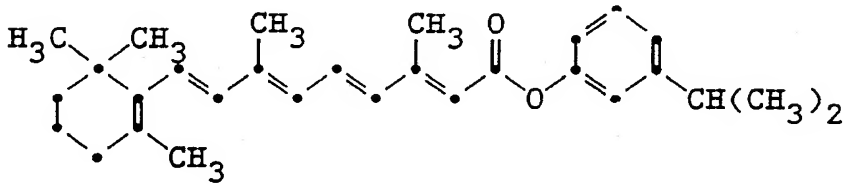

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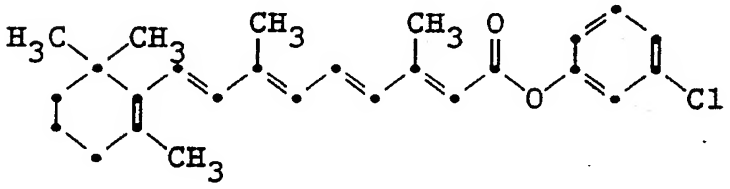

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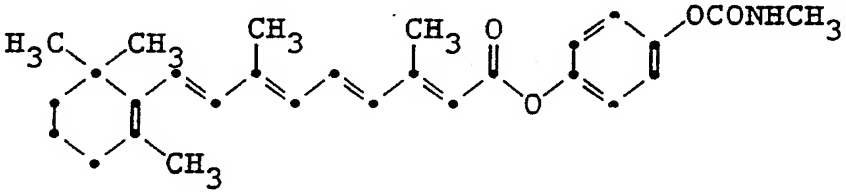

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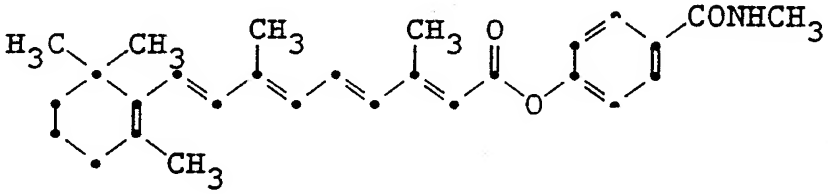

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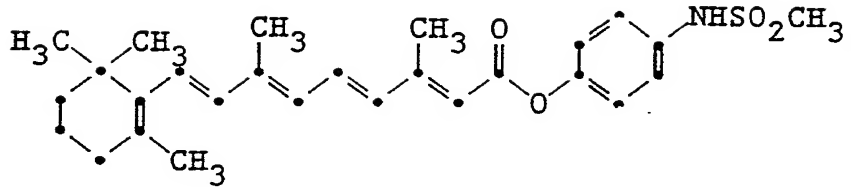
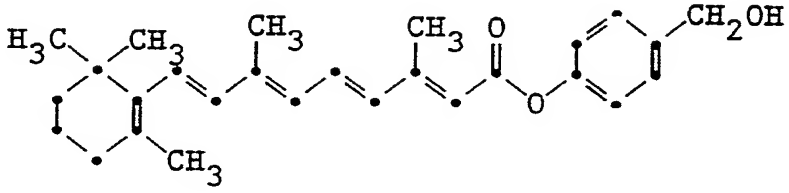


L.



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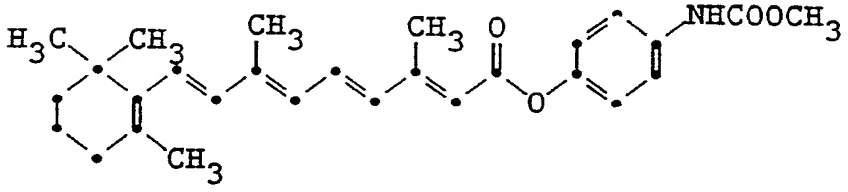

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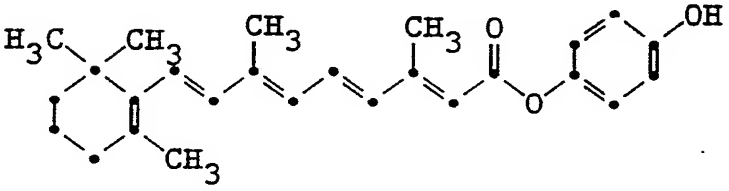


The therapeutic agents of this invention may be administered alone or in combination with pharmaceutically-acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets or capsules containing such excipients as starch, milk, sugar, certain of clay and so forth. They may be administered orally in the form of solutions which may contain coloring or flavoring agents. When applied topically for treatment of photoaging, they may be provided in the

form of dusting powders, aerosol sprays, ointments, aqueous compositions including solutions and suspensions, cream lotions and the like. In this regard, any of the commonly employed extending agents can be used depending on the nature of the product as is well-known in the art.

The physician will determine the dosage of the present theraputic agents which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary with the particular patient under treatment. He will generally wish to initiate treatment with small dosages substantially less than the optimum dose of the compound and increase the dosage by small increments until the optimum effect under the circumstances is reached.

The polyenes which are formulated in moisturizing bases such as creams or ointments, are usually used in low concentrations. For example, the compounds of the invention may be used in concentrations of about 0.001 percent to 10 percent and preferably about 0.01 percent to 5 percent by weight of the base.

In general, emollient or lubricating vehicles, such as oleaginous substances, which help hydrate the skin are preferred. As used herein, the term "emollient" will be understood to refer to the non-irritating character of the composition as a whole. That is, the nature of the vehicle and amount of polyene therein should be selected so as to provide a sub-irritating dose for topical application. Volatile vehicles which dry or otherwise harm the skin, such as alcohol and acetone, should be avoided.

An ointment base (without water) is preferred in the winter and in subjects with very dry skin. Examples of suitable ointment bases are

petrolatum, petrolatum plus volatile silicones, lanolin, and water in oil emulsions, such as Eucerin (Beiersdorf).

In warm weather and often for younger persons, oil in water emulsion (cream) bases, are preferred. Examples of suitable cream bases are Nivea Cream (Beiersdorf), cold cream (USP), Purpose Cream (Johnson & Johnson), hydrophilic ointment (USP), and Lubriderm (Warner-Lambert).

These topical compositions can contain any of the conventional excipients and additives commonly used in preparing topical compositions. Among the conventional additives or excipients which can be utilized in preparing these cosmetic compositions in accordance with this invention are preservatives, thickeners, perfumes and the like. In addition, the conventional antioxidants, such as butylated hydroxy-anisoles (BHA), ascorbyl palmitate, propyl gallate, citric acid butylated hydroxy toluene (BHT), ethoxy-quin and the like can be incorporated into these compositions. These topical compositions can contain conventional acceptable carriers for topical applications which are generally utilized in these compositions. These compositions may contain thickening agents, humectants, emulsifying agents and viscosity stabilizers, such as those generally uitilized. In addition, these compositions can contain flavoring agents, colorants, and perfume which are conventional in preparing cosmetic compositions.

The polyenes can be applied daily until the desired relief is obtained, and this may require one or two (or possibly three) applications each day, depending upon the particular individual. Normally the treatment requires at least a month. Thus, acne in its mildest form (only a small number of comedones) may be substantially cleared in four to six weeks. However, more severe cases may require three months or longer.

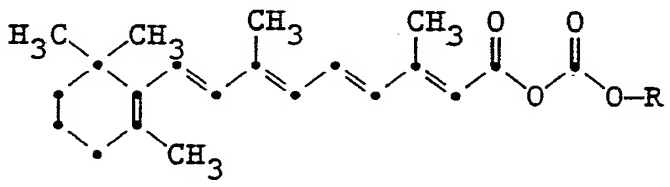
This invention is further illustrated by the following examples, which are illustrative only.

Example 1 Preparation of p-Acetamidophenyl Retinoate (Compound II)

Retinoic acid (0.010 mole) is dissolved in anhydrous tetrahydrofuran (75 ml) and treated at room temperature with triethylamine (0.011 mol). The solution is stirred for 5 minutes and ethyl chloroformate (0.011 mol) dissolved in anhydrous tetrahydrofuran (20 ml) is added dropwise with stirring. After one hour at room temperature, TLC (Silica gel/Pet ether/ether 3:10 shows only one spot with Rf = .8 (the carbonic anhydride of retinoic acid). Pentane (100 ml) is added and the triethylamine hydrochloride is collected by filtration. The filtrate is evaporated under vacuum (rotary evaporator) and the residual yellow oil is dissolved in anhydrous acetonitrile (75 ml). Acetamidophenol (0.010 mole) is added in one portion and the mixture is warmed to obtain a solution (≃30°C). Triethylamine (0.011 mole) is added in one portion followed by 4-dimethylaminopyridine (100 mg). The reaction becomes exothermic and carbon dioxide is evolved. It is stirred at 50°C for one hour then the yellow solid collected and air dried. Yield 92%, m.p. 200-202°C. TLC on silica gel shows one spot at origin eluting with 3:1 pet/ether and Rf = .3 redeveloping with ether alone. The product is recrystallized from acetonitrile. If the product does not crystallize from the acetonitrile reaction mixture, evaporate to an oil and crystallize from mixtures of ethanol-water.

Compounds III-XI, XVII, XIX-LII were prepared by analogous synthetic routes.

The intermediate carbonyl anhydride of the example has the structure



wherein

R is $-C_2H_5$.

The following analytical data found and calculated for compounds II-XI, XVII, XIX, XXI, XXIII, XXXI, XXXII, XXXIII, XXXIV, XLIV and XLVI are as follows:

Compound	FOUND C	H	N	Cl	CALCULATED C	H	N	Cl
II	77.3	7.8	3.0		77.6	8.1	3.2	
III	77.4	7.9			77.4	7.9		
IV	76.0	7.8	3.2		80.8	7.8	3.5	
V	79.9	8.4			79.8	8.4		
VI	81.1	8.8	3.0		81.5	8.8	3.0	
VII	75.7	7.5			76.0	7.6		
VIII	81.8	8.7			83.7	8.9		
IX	77.2	7.6	3.0		79.5	7.7	2.9	
X	77.7	6.9	2.8		77.8	6.9	2.8	
XI	79.8	6.7	2.4		81.4	7.2	2.6	
XVII	74.0	7.4	3.1		74.1	7.4	3.3	
XXIII	77.06	8.00	3.33		77.29	7.93	3.34	
XIX	77.05	7.92	3.30		77.29	7.93	3.34	
XXXI	80.52	7.85	3.48		80.76	7.78	3.49	
XXXII	82.69	8.58	—		82.74	8.57	—	
XXI	76.47	8.55	3.13		77.29	7.93	3.34	
XXXIII	76.88	8.17	3.22		77.56	8.14	3.23	
XXXIV	80.61	7.83	3.44		80.76	7.78	3.49	
XLIV	76.44	7.77			76.74	8.11	—	
XLVI	75.85	7.63		8.67	75.48	7.60	—	8.63

Example 2 Effect of Compounds on Rhino Mouse Utriculi Diameter

In the rhino mouse test, polyene compounds related to Vitamin A, including all—trans retinoic acid, are highly effective in reducing the size of horn—filled utricles in hairless mouse skin (Mezick et al, "Topical and Systemic Effects of Retinoids on Horn—Filled Utriculus Size in the Rhino Mouse. A Model to Quantify 'Anti—keratinizing' Effects of Retinoids", J. Invest. Dermatol., 1984; 83:110—113). Hairless rhino mice $hr^{rh}hr^{rh}$) were treated with 0.05 ml of Compounds I—XIV, all—trans retinoic acid or the ethanol vehicle on the dorsolateral skin once daily on five consecutive days for one week. Mice were sacrificed by CO_2 asphyxiation on the third day after the last treatments. A 7/8" full thickness punch biopsy of skin was removed and placed in a 0.5 percent acetic acid overnight at 4°C. The following day, epidermal sheets were removed from the dermis by peeling with a metal spatula. These sheets were fixed in formalin, dehydrated with ethanol, and kept in xylene.

To assess utricle diameter, each epidermal sheet was placed on a glass slide in a few drops of xylene. The diameter of 20 utricles was measured with an image analyzer. The effect of Compounds I—XIV and all—trans retinoic acid on utriculi diameter is shown in Table 1.

The dose—related response in the rhino mouse test of selected compounds is shown in Table 2. The ED_{30} values shown were calculated by interpolation of the regression lines of the log concentration—percent reduction plots.

Table 1

The Effect of Compounds on
Rhino Mouse Utriculi Diameter

Compound	Concentration Percent (W/V) in Ethanol	Utriculi Reduction vs. Ethanol (Percent)
I	0.1	Not Done
II	0.1	48
III	0.1	51
IV	0.1	55
V	0.1	43
VI	0.1	45
VII	0.1	48
VIII	0.1	56
IX	0.16	52
X	0.1	9
XI	0.17	44
XII	0.1	44
XIII	0.1	43
XIV	0.1	41
trans-Retinoic Acid	0.01	52

Table 2

Dose-Related Activity of
Selected Compounds and All-Trans Retinoic Acid
on Rhino Mouse Utriculi Diameter

Compound Part I	Concentration Percent (W/V) in Ethanol	Utriculi Diameter Reduction (Percent)	ED_{30} (mM)	Global Irritation
II	0.01	50	0.03	
	0.001	38		
	0.0001	6		
III	0.1	51	0.14	
	0.01	43		
	0.001	10		
IV	0.1	55	0.13	
	0.01	44		
	0.001	10		
V	0.1	43	0.12	
	0.01	36		
	0.001	21		
VI	0.1	45	0.56	
	0.01	14		
	0.001	6		
VII	0.1	48	0.20	
	0.01	30		
	0.001	16		
VIII	0.1	56	0.27	
	0.01	26		
	0.001	2		
trans-Retinoic Acid	0.1	52	0.020	
	0.01	37		
	0.001	18		

Table 2(continued)

Dose-Related Activity of

Selected Compounds and All-Trans Retinoic Acid

on Rhino Mouse Utriculi Diameter

Part II				
	II	0.1	0.037	1.65
	XIX	0.1	0.120	2.5
	XX	0.1	0.074	4.5
	XXI	0.1	0.074	
	XXII	0.1	0.048	
	XXIII	0.1	0.159	
	XXIV	0.1	0.249	
	XXV	0.1	0.229	3.3
	XXVI	0.1	0.393	3.3
	XXVII	0.1	0.310	6.6
	XXVIII	0.1	0.275	6.6
	XXIX	0.1	0.239	
	XXX	0.1	0.229	
	XXXI	0.1	0.131	7.3
	XXXII	0.1	0.338	
	XXXIII	0.1	0.196	
	trans-Retinoic Acid	0.1	0.015	6.6

For the purposes of this invention, Global Irritation score is defined as the sum of erythema, edema and scaling scores. A description of erythema, edema and scaling scores for Compound II is described as follows:

A rabbit model of skin irritation was used to assess the dermatitis produced by treatment with Compound II and all-trans retinoic acid. The rabbit is commonly used as a skin irritation model for predicting the potential local irritation of topically applied materials.

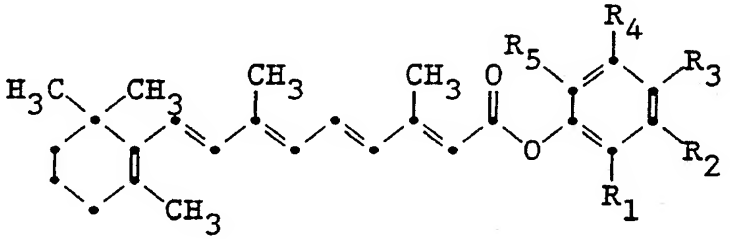
New Zealand albino rabbits, from Beckens Farms, Sanborn, NY, were clipped closely at four sites on the back with an electric hair clipper to give 4 cm X 4 cm square sites. Each rabbit received 0.2 ml of Compound II and all-trans retinoic acid, once daily for fourteen consecutive days. Each day, the degree of erythema, scaling and edema was assessed visually by using the Draize 0 to 4 grading method. The results were expressed as average daily Draize score, which was derived by taking the cumulative score over fourteen days, for each parameter, and dividing by fourteen.

This procedure was followed to obtain the Global Irritation scores provided above.

The invention has been described in detail with particular reference to preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

What is claimed is:

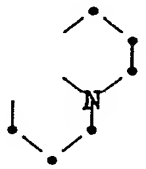
1. A method of treating acne or psoriasis comprising administering a compound having the structure:



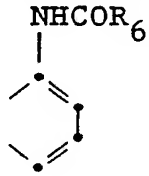
wherein

R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of H, Cl, straight or branched alkyl of 1 to 10 carbon atoms, NO_2, $COOR_6$, CN, OR_6, NR_6R_7, $NR_6C(=S)NR_7R_8$, NR_6COR_7, $SO_2NR_6R_7$, $CH(CH_3)COOH$, $CONR_6R_7$, COR_6, $OCONR_6R_7$, NR_6COONR_7, R_9OR_6, $NR_6SO_2R_7$, $Si(CH_3)_3$, and $NR_6CONR_7R_8$,

R_3 together with R_4 forms a benzo ring or taken together with R_2 forms a benzo or tetrahydrobenzo ring or together with R_2 and R_1 forms a:

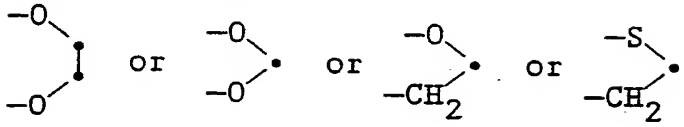


moiety or together with R_2 forms a



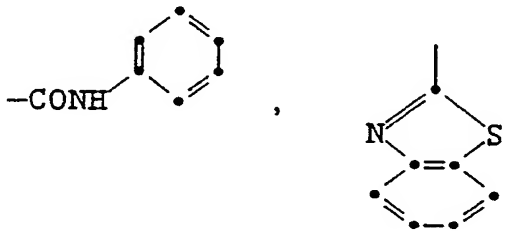
moiety or R_2 together with R_1 forms a benzo ring

or R_2 together with R_3 forms a



moiety, or

R_1 is independently selected from the group consisting of



moiety,

R_6, R_7 and R_8 are independently selected from the group consisting of straight or branched alkyl containing from 1 to 10 carbon atoms, aryl containing from 6 to 10 carbon atoms and hydrogen, and

R_9 is alkylene of 1 to 6 carbon atoms, and iron carbonyl complexes thereof,

to an area of the human skin in an amount effective to repair damage due to acne or psoriasis.

2. The method of claim 1 wherein R_2 and R_3 are independently selected from the group consisting of NR_6COR_7, $CONR_6R_7$, $SO_2NR_6R_7$, $OCONR_6R_7$, NR_6COOR_7, $NR_6CONR_7R_8$, $NR_6SO_2R_7$ and $NR_6C(=S)NR_7R_8$.

3. The method of claim 1 wherein the compound is mixed with a therapeutically and pharmaceutically acceptable carrier material.

4. The method of claim 1 wherein the compound is applied topically.

5. The method of claim 1 wherein the compound is applied by oral administration.

6. The method of claim 1 wherein R_3 is $NHCOCH_3$ and R_1, R_2 and R_4 are H.

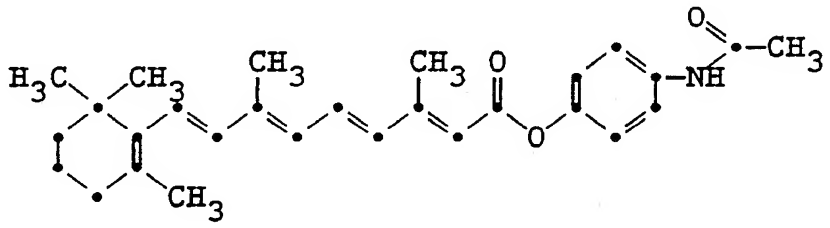
7. The method of claim 1 wherein the compound comprises about 0.001 percent to about 10 percent by weight of the mixture applied.

8. The method of claim 1 wherein the compound comprises about 0.01 percent to about 5 percent by weight of the mixture applied.

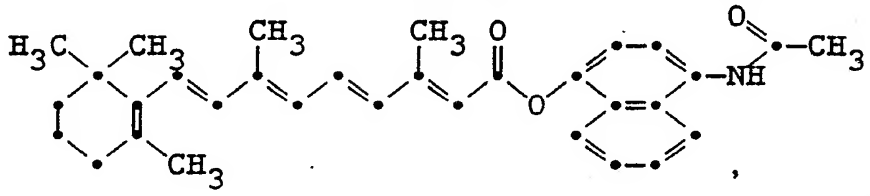
9. The method of claim 3 wherein the compound is applied to human skin.

10. The method of claim 1 wherein R^3 is $NHCOCH_3$ and R^1, R^2 and R^4 are H.

11. The method of claim 1 wherein the compound is:



12. The method of claim 1 wherein the compound is selected from the group consisting of



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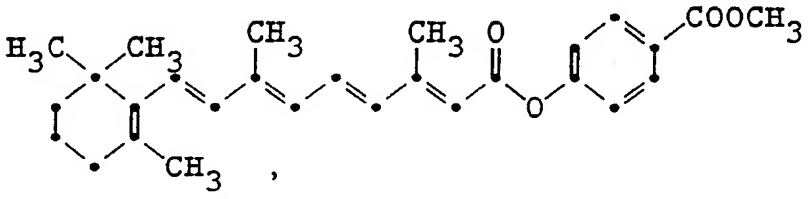

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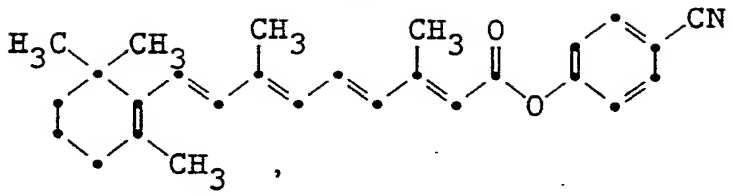
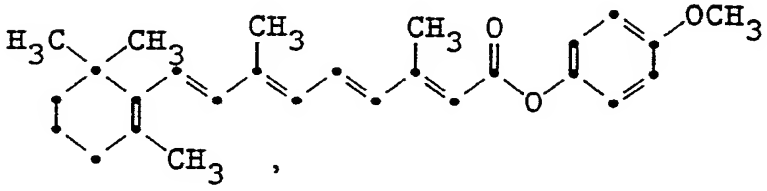
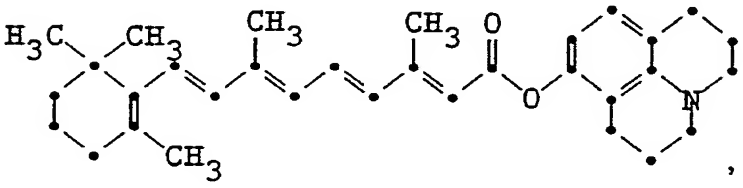
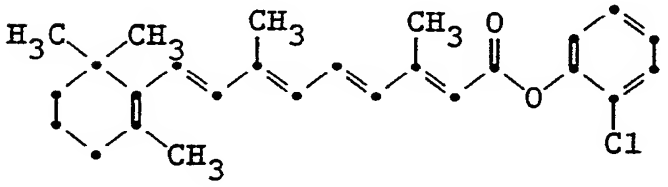
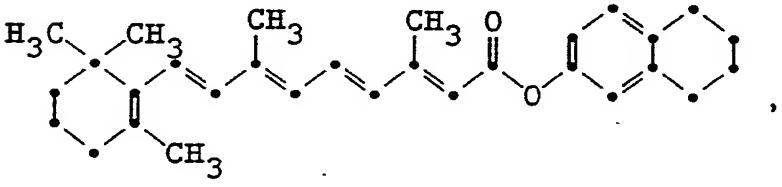
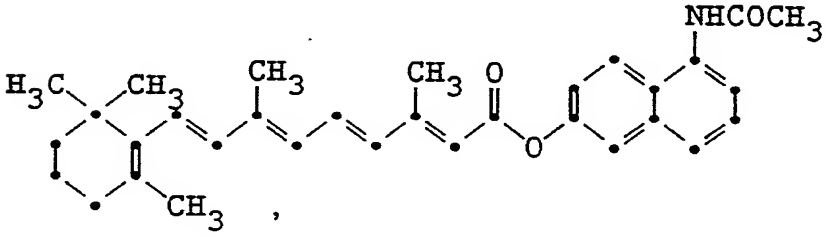


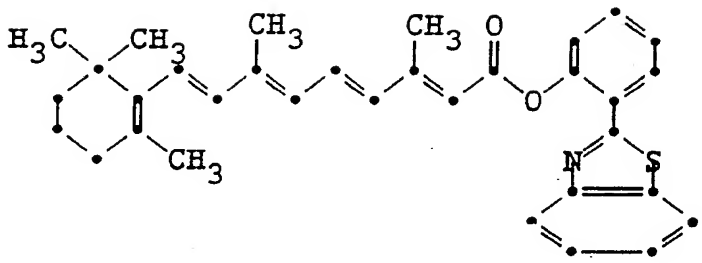


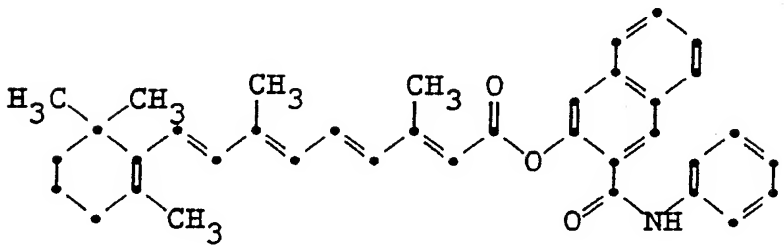


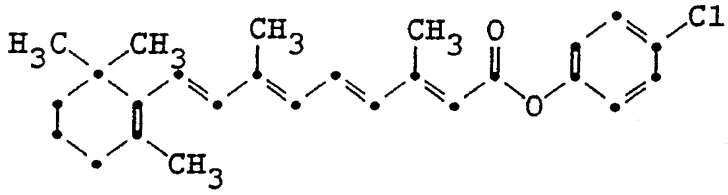


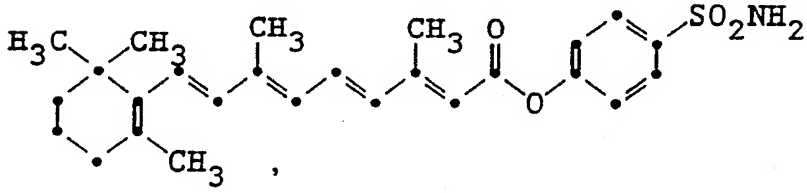


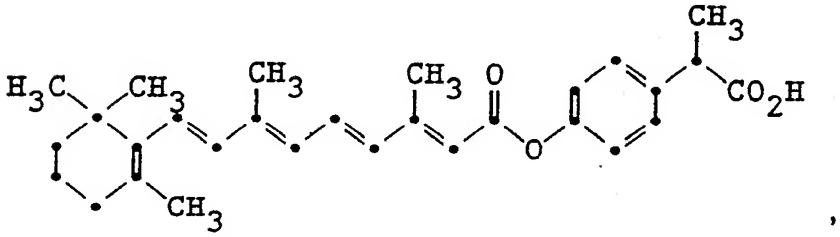


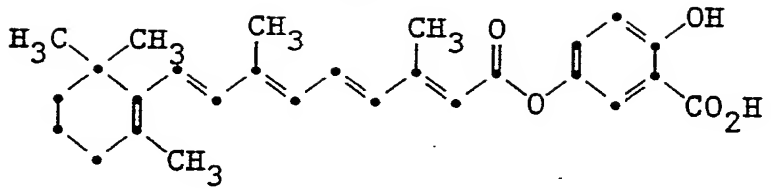


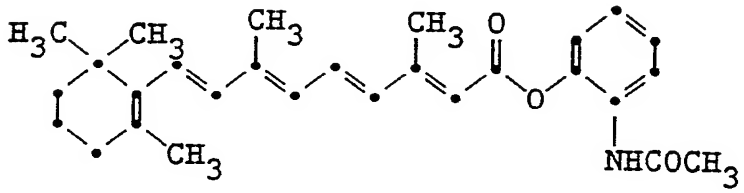


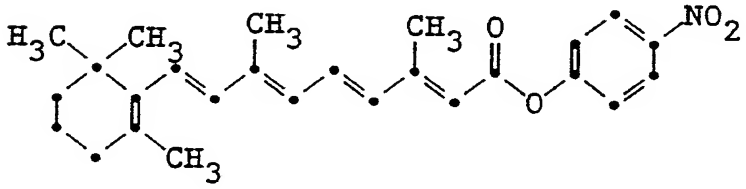


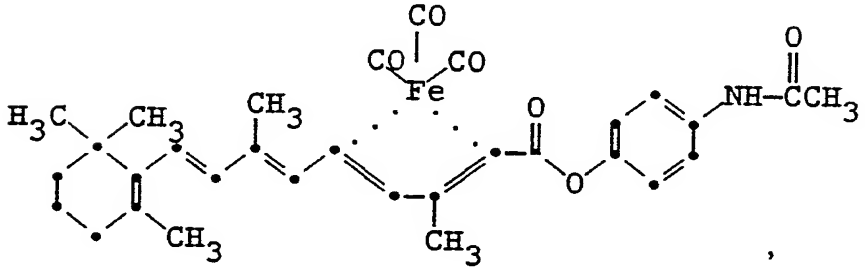


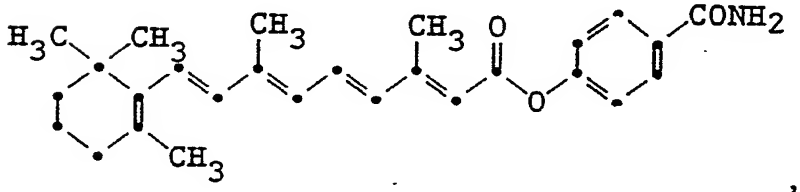


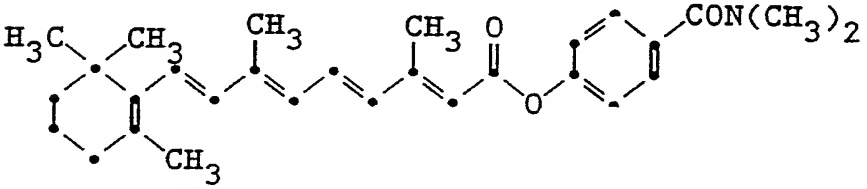


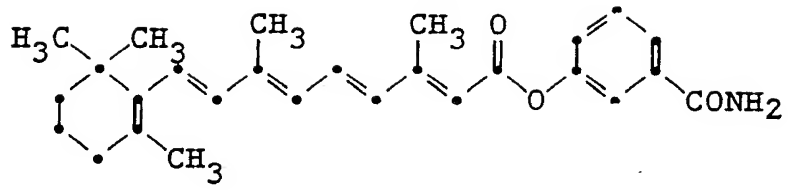


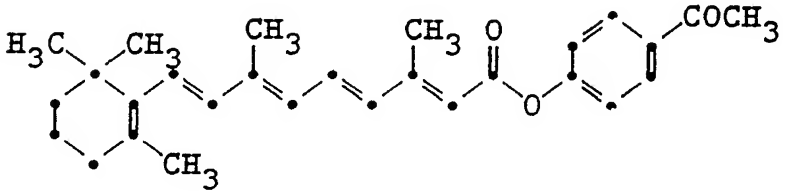


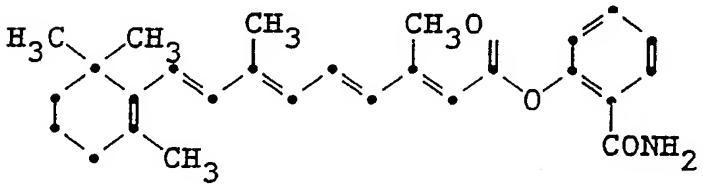


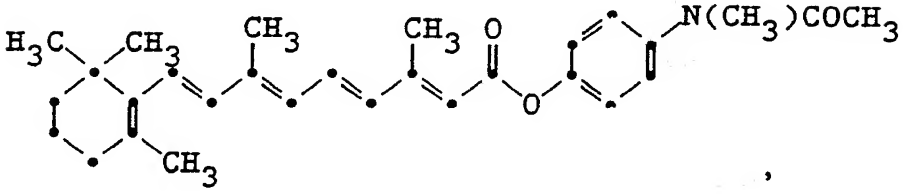


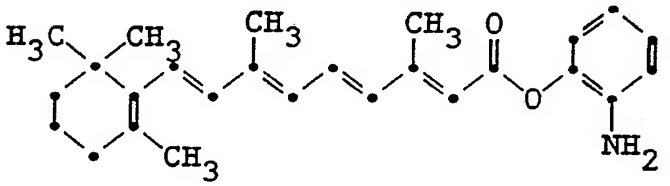


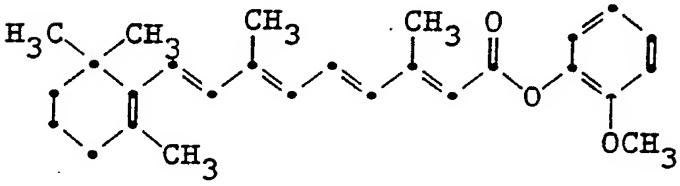


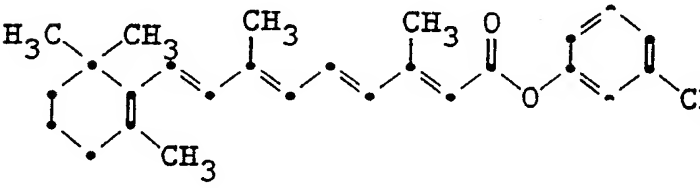


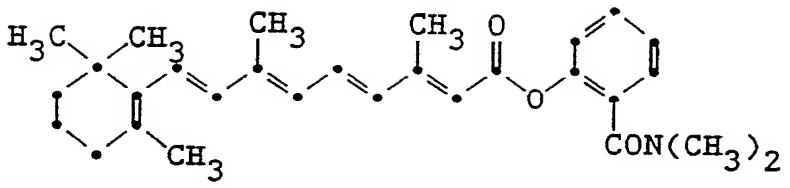




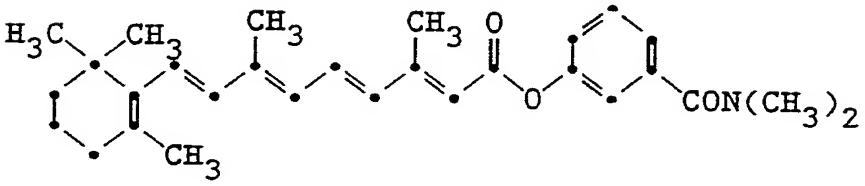




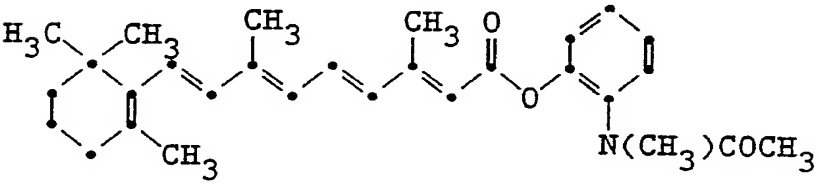



H3C
CH3
CH3
CH3
O
O
CH3
CON(CH3)2

,


H3C
CH3
CH3
CH3
O
O
CH3
CON(CH3)2

,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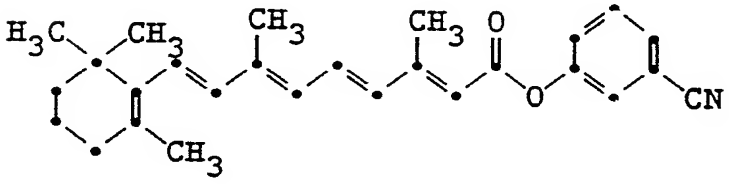
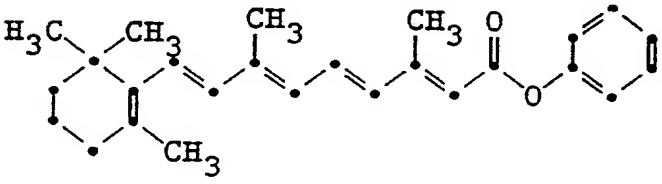
CH3
CH3
CH3
O
O
CH3
N(CH3)COCH3

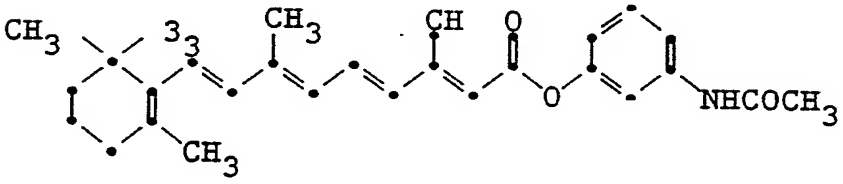
,


H3C
CH3
CH3
CH3
O
O
CH3
CN

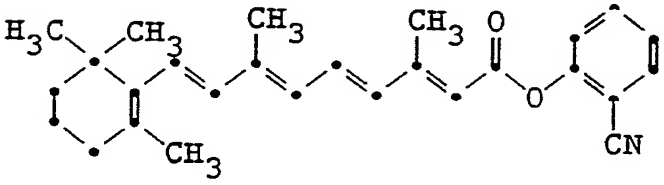
,


H3C
CH3
CH3
CH3
O
O
CH3

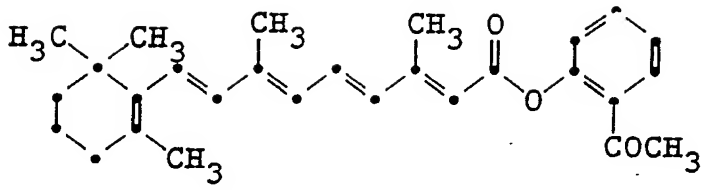
,

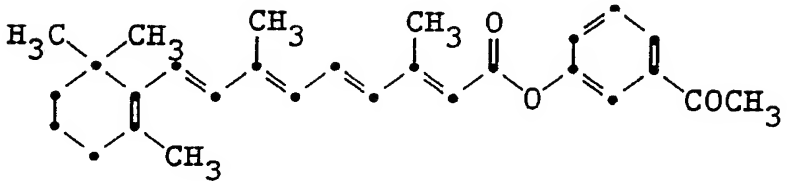

CH3
3
3
CH3
CH
O
O
CH3
NHCOCH3

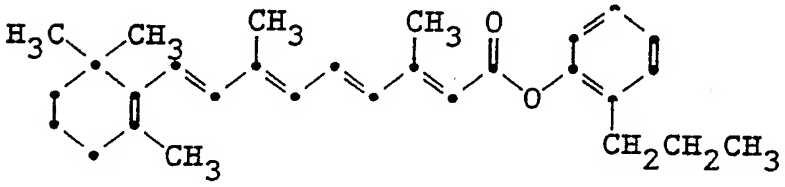
,

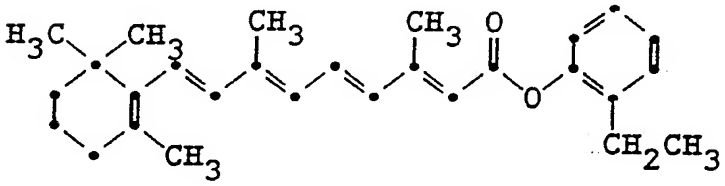

H3C
CH3
CH3
CH3
O
O
CH3
CN

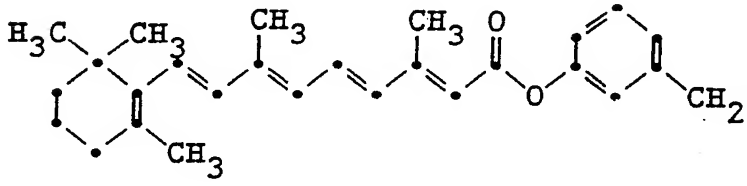
,

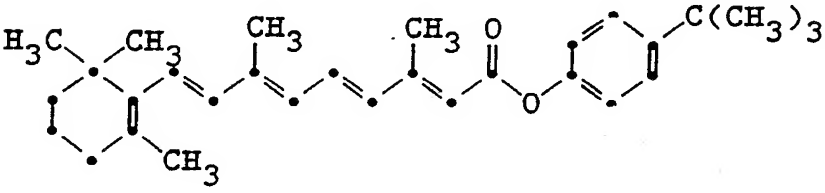


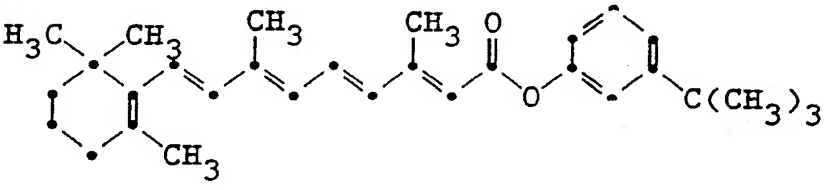


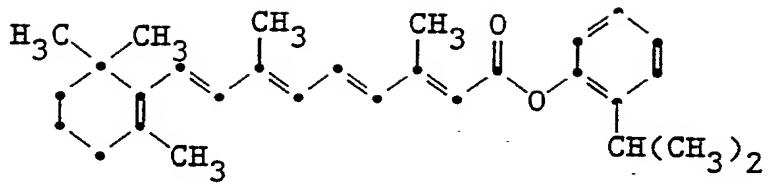


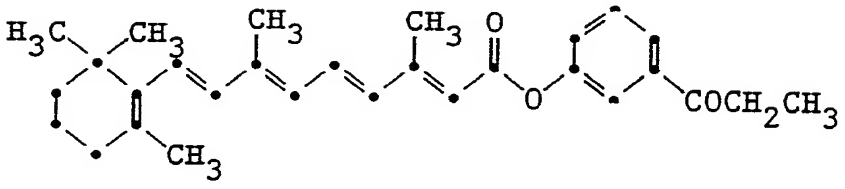


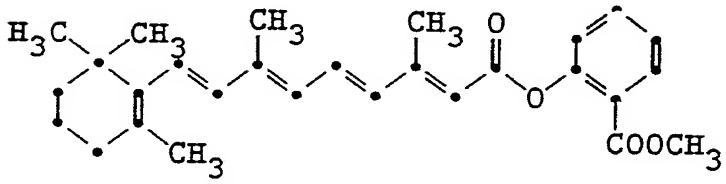


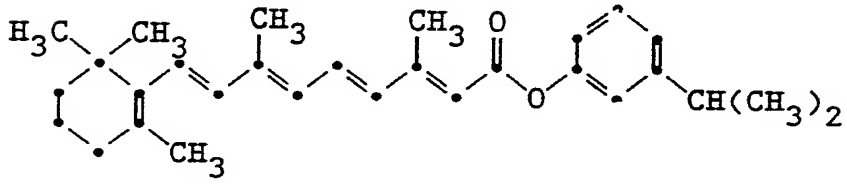


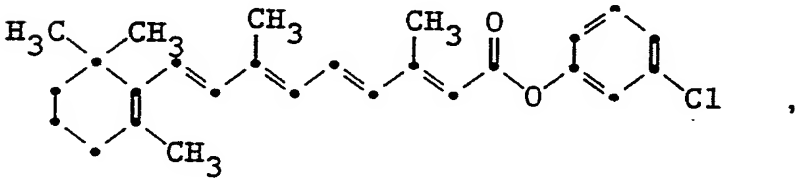


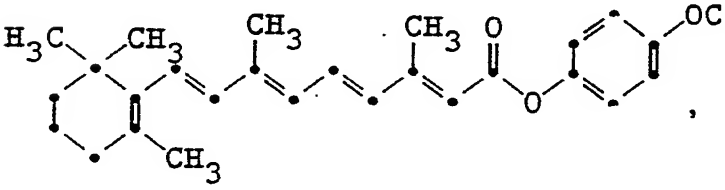


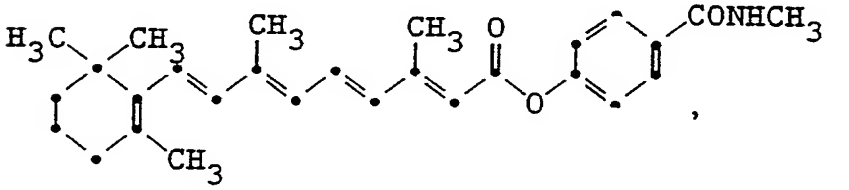


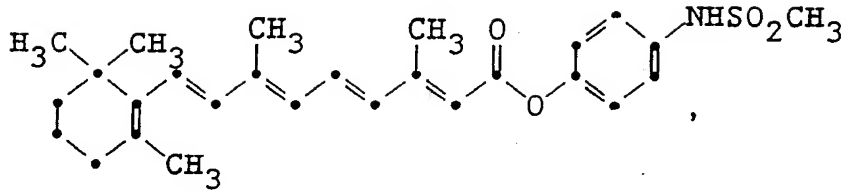


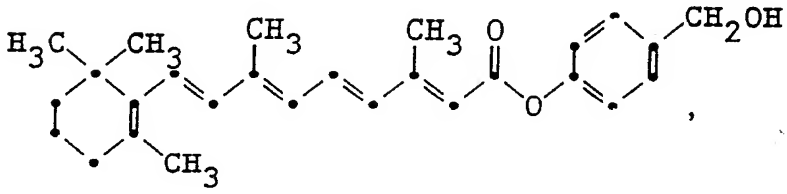


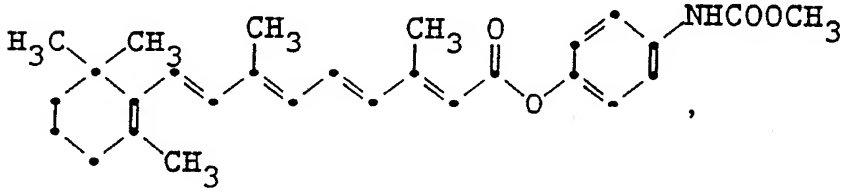


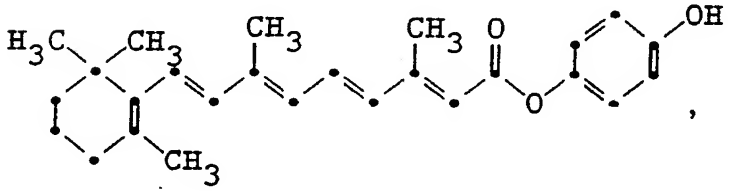




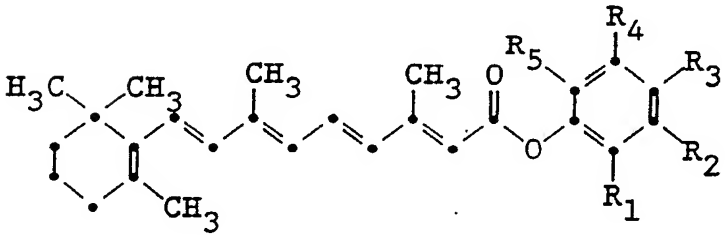








13. A compound having the structure:



wherein

R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of H, Cl, NO_2, CN, OR_6, $NR_6C(=S)NR_7R_8$, $SO_2NR_6R_7$, $CH(CH_3)COOH$, $OCONR_6R_7$, NR_6COONR_7, R_9OR_6, $NR_6SO_2R_7$, $Si(CH_3)_3$, $NR_6CONR_7R_8$,

NR_6COR_7, with the proviso that where R_3 is $NHCOR_7$, and R_1 and R_2 are hydrogen, R_7 cannot be methyl,

straight or branched alkyl of 1 to 10 carbon atoms, with the proviso where R_1 is alkyl, the alkyl cannot contain an acetal,

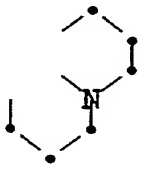
$COOR_6$, with the proviso that where R_1 is $COOR_6$, R_6 is not hydrogen or methyl, and that where R_3 is $COOR_6$, R_6 is not ethyl,

NR_6R_7, with the proviso that where R_1 or R_3 are NR_6R_7, R_6 and R_7 are not both hydrogen,

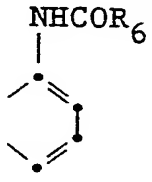
$CONR_6R_7$, with the proviso that where R_1 is $CONR_6R_7$, R_6 and R_7 are not both hydrogen, and ,

COR_6, with the proviso that where R_3 is COR_6, R_6 is not hydrogen,

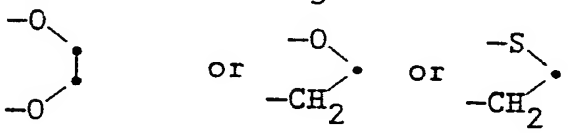
R_3 together with R_4 forms a benzo ring or taken together with R_2 forms a benzo or tetrahydrobenzo ring or together with R_2 and R_1 forms a:



moiety or together with R_2 forms a

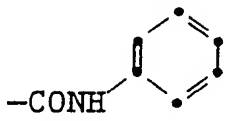


moiety or R_2 together with R_1 forms a benzo ring or R_2 together with R_3 forms a

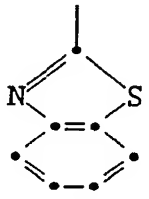


moiety, or

R_1 is independently selected from the group consisting of



,



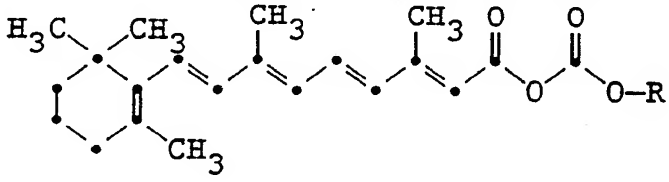
moiety,

R_6, R_7 and R_8 are independently selected from the group consisting of straight or branched alkyl containing from 1 to 10 carbon atoms, aryl containing from 6 to 10 carbon atoms and hydrogen, and

R_9 is alkylene of 1 to 6 carbon atoms, and iron carbonyl complexes thereof.

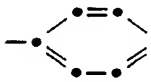
14. The compound of claim 13 wherein R_2 and R_3 are independently selected from the groups consisting of NR_6COR_7, $CONR_6R_7$, $SO_2NR_6R_7$, $OCONR_6R_7$, NR_6COOR_7, $NR_6CONR_7R_8$, $NR_6SO_2R_7$ and $NR_6C(=S)NR_7R_8$.

15. A compound having the structure:

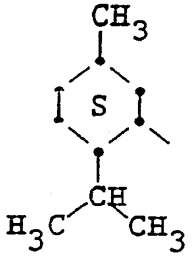


wherein

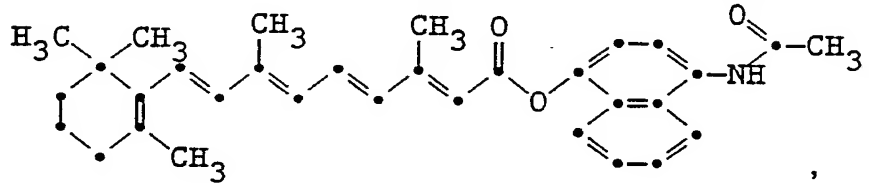
R is $-C_2H_5$, $-CH_2CF_3$, $-CH=CH_2$,

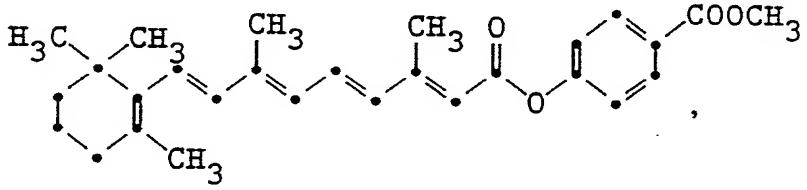


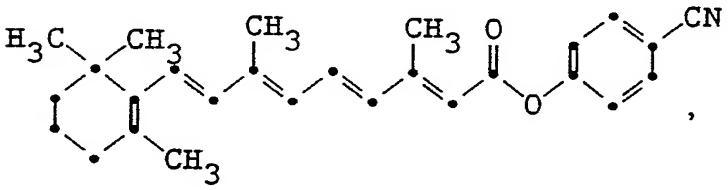
, or

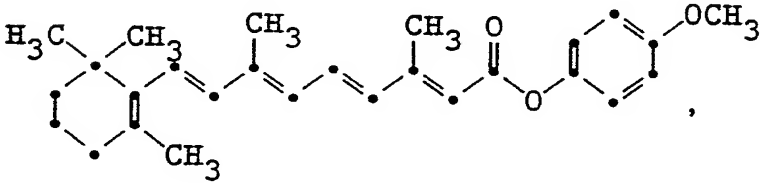


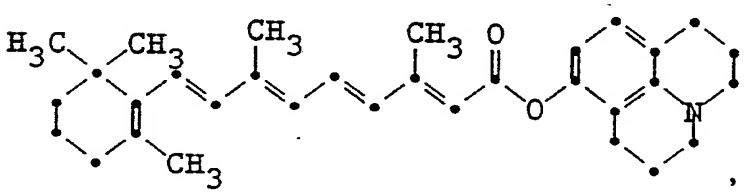
16. A compound of claim 13 selected from the group consisting of the following structures:

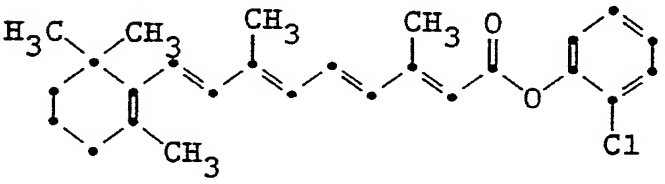


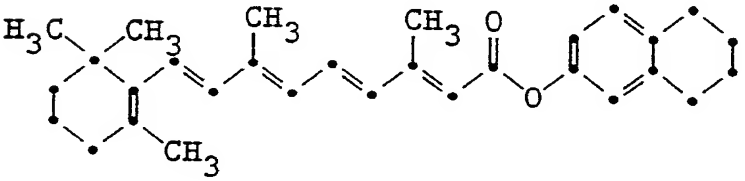


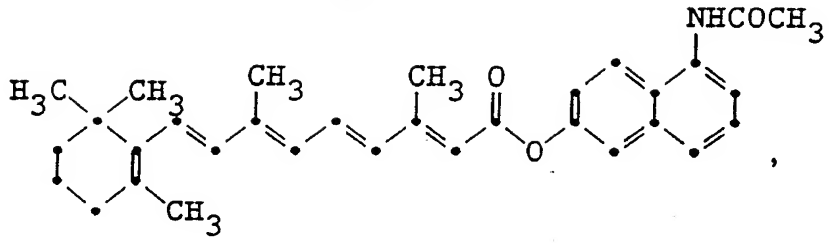


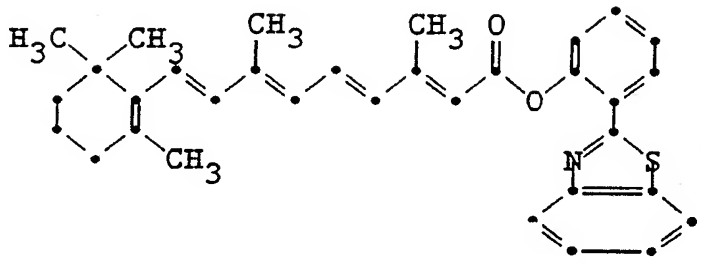


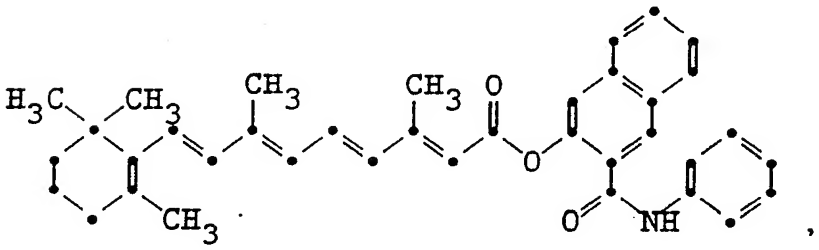


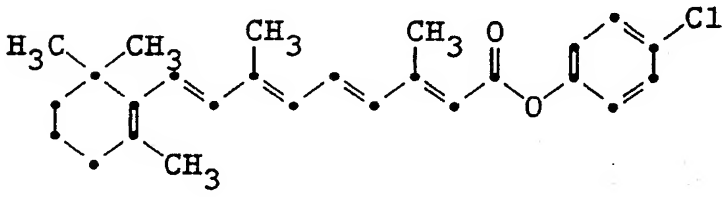


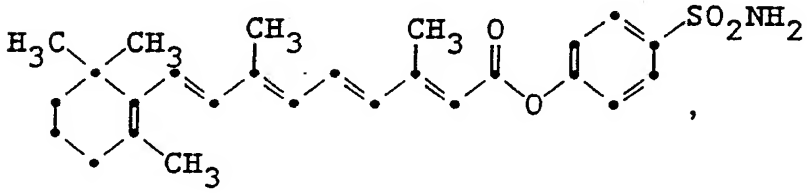


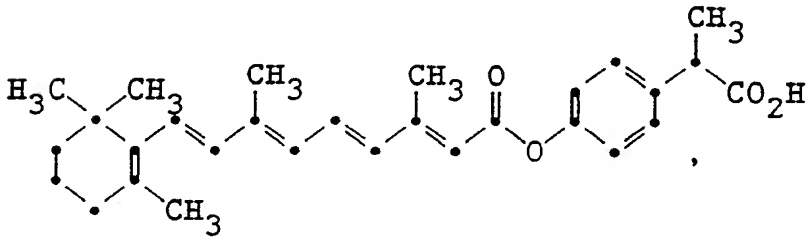


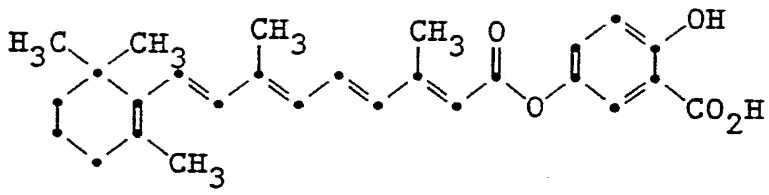


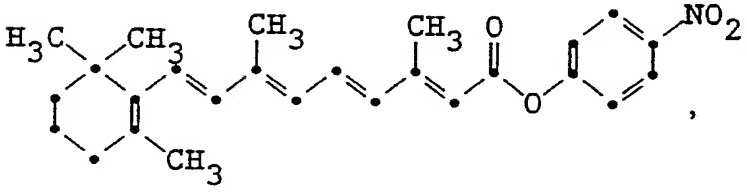


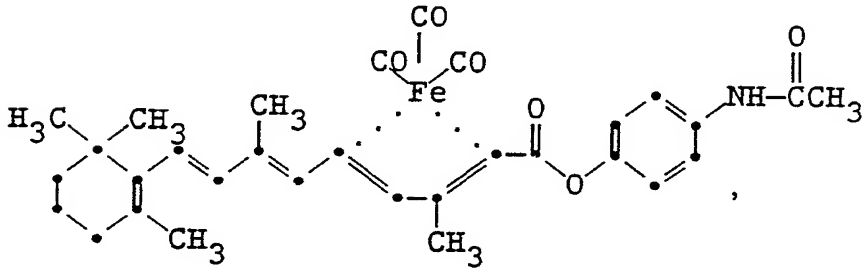


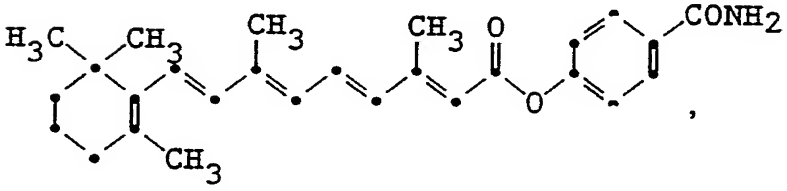


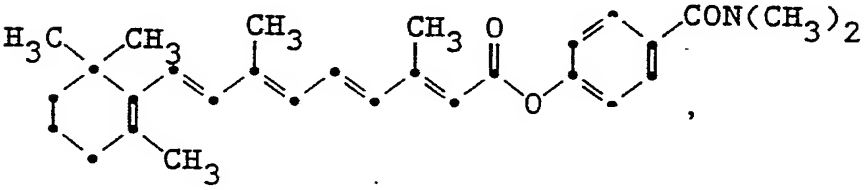


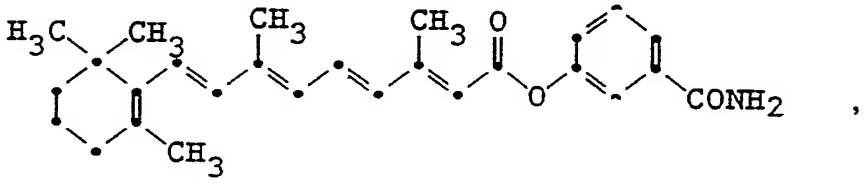


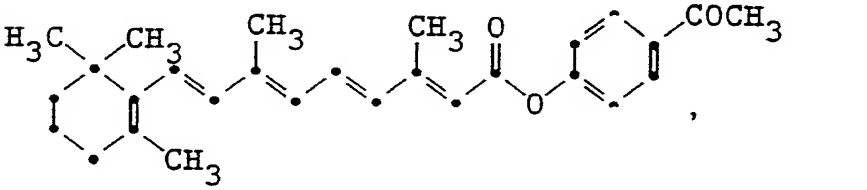


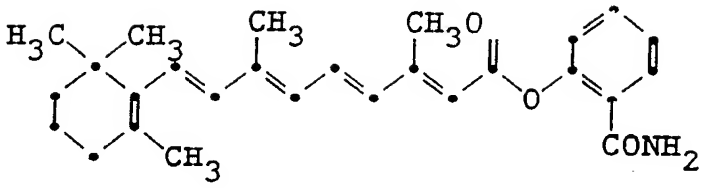


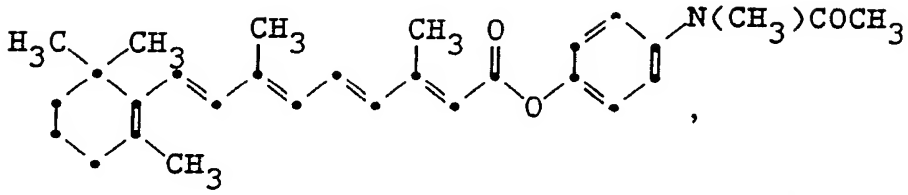


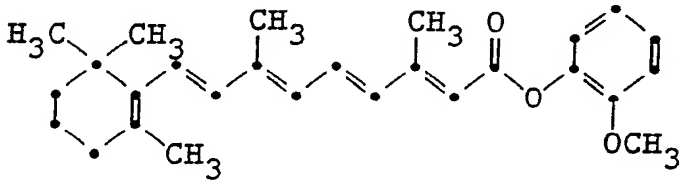


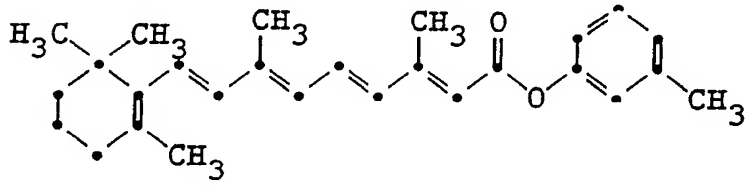


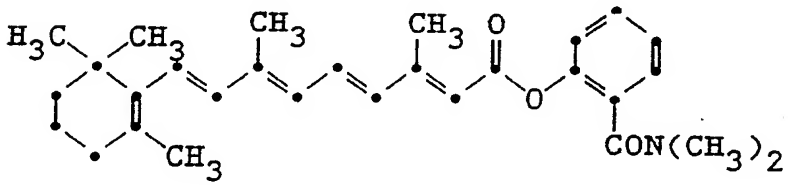


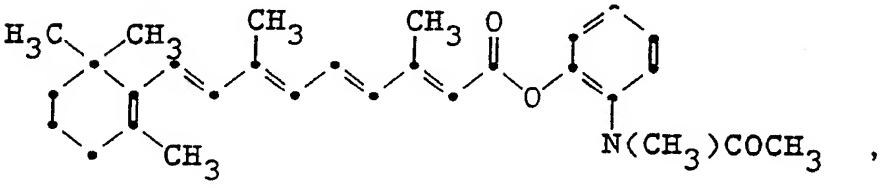


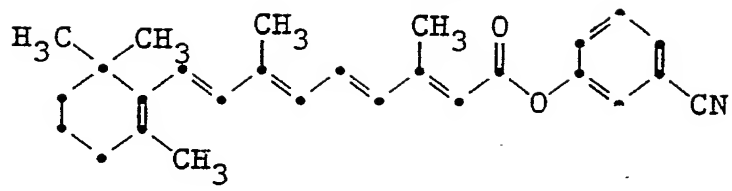


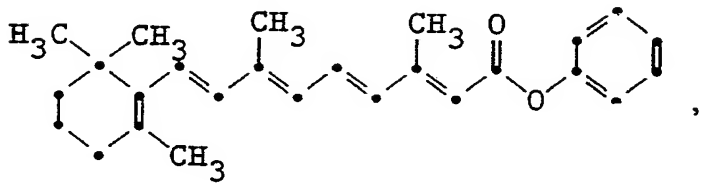


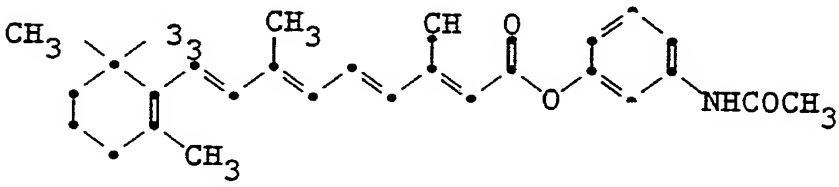


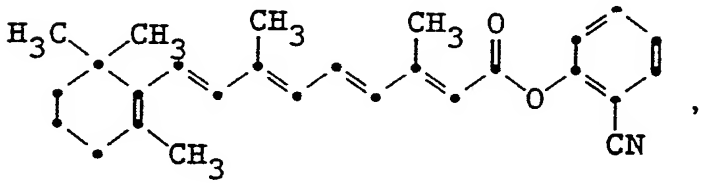


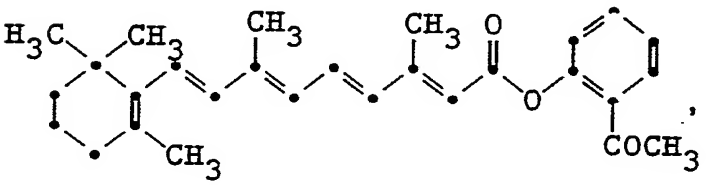


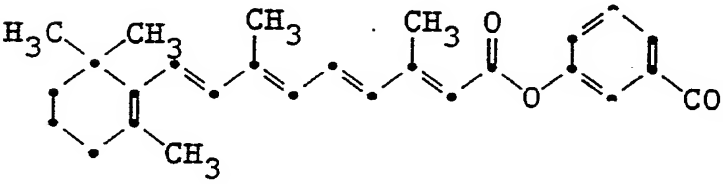


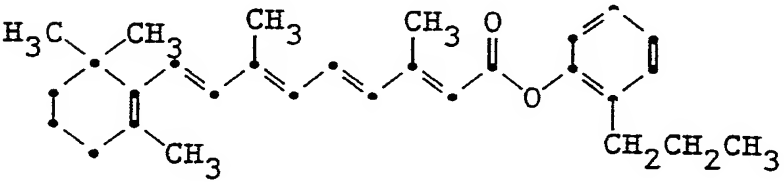


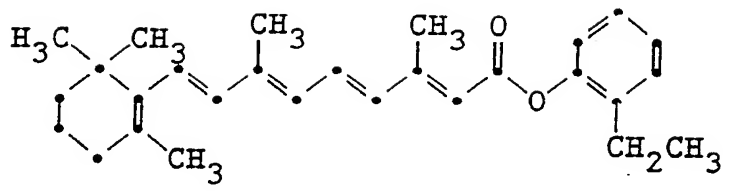


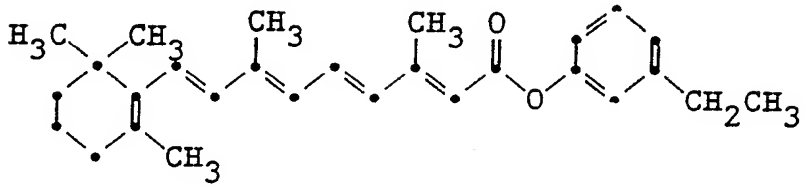


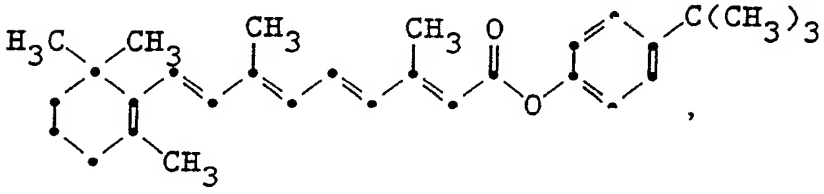


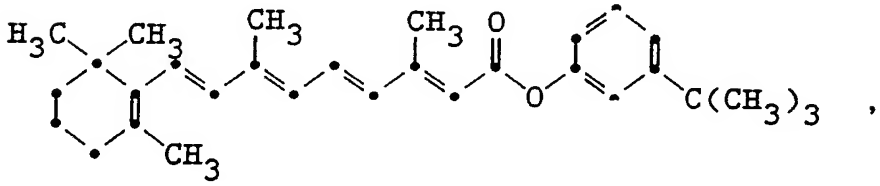


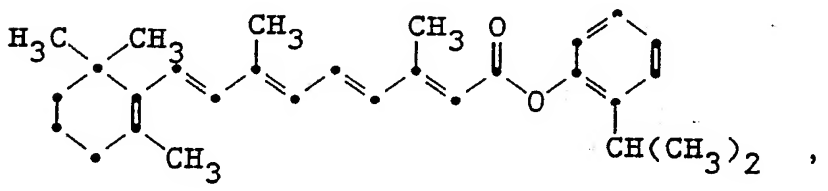


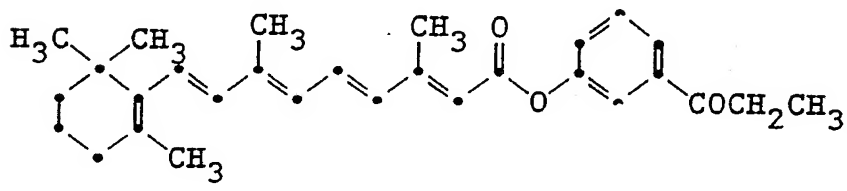


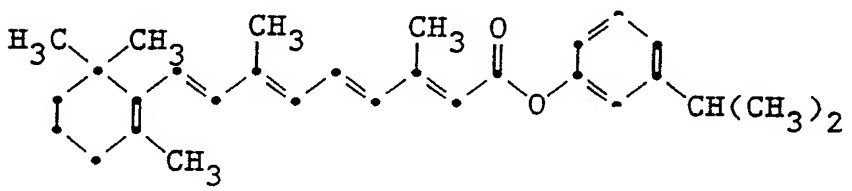


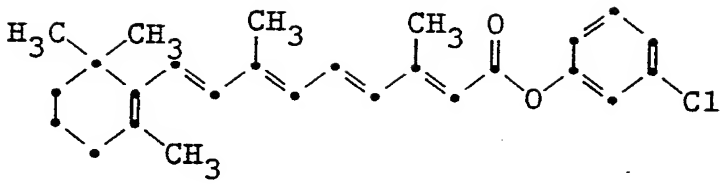








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CH3

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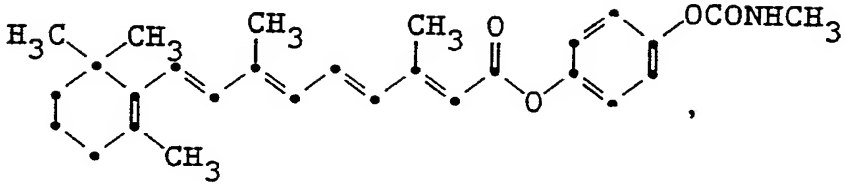
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CH3

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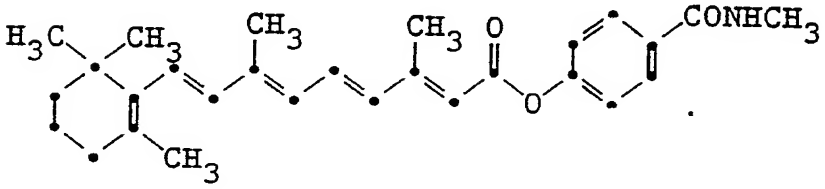
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O
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CH3

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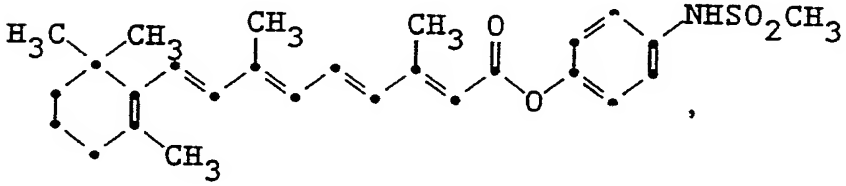
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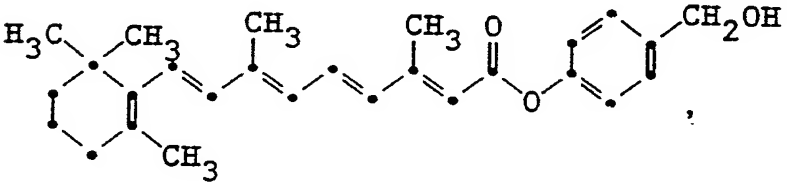
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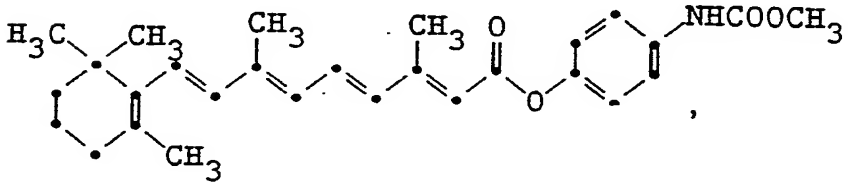
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CH3
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O
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CH3

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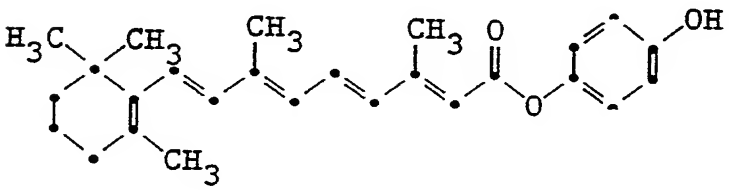
H3C
CH3
CH3
CH3
O
O
OH
CH3

International Application No. PCT/US 90/04051

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	agents. Synthesis of derivatives of retinoic acid", see page 723, abstract 123037g & Yaoxue Xuebao 1981, 16(9), 678-86 --	
A	FR, A, 2436602 (YU, Ruey Jiin et al.) 18 April 1980 see examples 11,16,17 --------	13,16

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 1-12 because they relate to subject matter not required to be searched by this Authority, namely:

see: PCT rule 39.1(IV); methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9004051 SA 39219

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/11/90
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 4595696	17-06-86	None		
FR-A- 2212329	26-07-74	CH-A-	601217	30-06-78
		DE-A-	2354792	09-05-74
		GB-A-	1443993	28-07-76
		GB-A-	1443994	28-07-76
		GB-A-	1443992	28-07-76
		JP-A-	49076838	24-07-74
		US-A-	3928400	23-12-75
FR-A- 2436602	18-04-80	US-A-	4216224	05-08-80
		DE-A-	2938041	03-04-80
		GB-A-	2033747	29-05-80